Minnesota State Medical Association
100th Annual Session—May 18-20, 1953
Saint Paul, Minnesota

Minnesota MEDICINE

PUBLISHED MONTHLY BY THE MINNESOTA STATE MEDICAL ASSOCIATION

Volume 35 NOVEMBER, 1952 Number 11

Printed in U.S.A. 40c a copy—$3.00 a year

Minnesota Medicine

Journal of the Minnesota State Medical Association, Southern Minnesota Medical Association, Northern Minnesota Medical Association, Minnesota Academy of Medicine and Minneapolis Surgical Society

Volume 35 **November, 1952** **Number 11**

Contents

Entered at the Post Office in Saint Paul as second class mail matter. Accepted for mailing at the special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 13, 1918.

MINNESOTA MEDICINE

OFFICIAL JOURNAL OF THE MINNESOTA STATE MEDICAL ASSOCIATION

Published by the Association under the direction of its Editing and Publishing Committee

Office of Minnesota State Medical Association,
496 Lowry Medical Arts Bldg., Saint Paul 2, Minnesota.

Annual Subscription—$3.00. Single Copies—$0.40. Foreign and Canadian Subscriptions—$3.50.

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MODERN TRENDS IN THE TREATMENT OF GOITER

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THIS BRIEF presentation represents a survey, necessarily personalized, of current thinking on the subject.

Primary Hyperthyroidism (Exophthalmic Goiter, Graves' Disease)

The fundamental defect in this disorder remains undetermined. The wise physician will make those personal and environmental readjustments that seem indicated while directing the course and follow-up of therapy aimed at the thyroid gland. He realizes that while present-day therapy is successful, thyroid dysfunction is probably not the primary defect and that a definite recurrence rate exists. The longer any large series is followed the greater will be the incidence of recurrence.

The last ten years have witnessed the introduction of two new means of therapy—radio-active iodine and anti-thyroid drugs. Control can now be achieved by: (1) medical management with radio-active iodine; (2) medical management with anti-thyroid drugs; (3) subtotal thyroidectomy after preoperative preparation with anti-thyroid drugs, iodine and an adequate program of diet and rest.

Radio-active iodine seems, after a ten-year follow-up, to induce a remission of the same type and permanence and in the same percentage of patients with exophthalmic goiter as does subtotal thyroidectomy.[12] It has the following additional advantages:

1. It can be given in a drink of water.
2. The discomfort and expense of operation are obviated.
3. The prolonged use of medicine is not necessary.
4. The two major complications of thyroidectomy—parathyroid tetany and vocal cord paralysis—are avoided.

At the present time two distinct disadvantages restrict its use: (1) the possible hazard of late carcinogenesis and around this revolve all the disadvantages inherent in the unknown; (2) the expense of the apparatus and the personnel necessary for the use of the material, as well as its relative unavailability except in the major centers. In addition, there is some danger to the severely toxic patient in the exacerbation occasionally seen in the first few days after treatment. This is thought to be due to the release of hormone from the damaged thyroid cells.

The hazard of excessive irradiation is known, but how this applies to the dosage range of radio-active iodine and the thyroid gland remains unknown. Widely different opinions are held by well qualified men.[6] The data upon which to base an accurate judgment are not available at the present time and will only be available after approximately another decade of careful follow-up of patients who have been so treated. On the basis of the known development of malignancy in other tissues with the use of other types of irradiation, it does seem likely that fifteen to twenty years would be the expected time lapse. With this in mind, the use of radio-active iodine in the treatment of patients with a life expect-

From the Department of Medicine, The Duluth Clinic, Duluth, Minnesota.

Read in the Symposium on Therapy at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

ancy that falls within this range appears to be justified.

Anti-thyroid drugs—propylthiouracil, methylthiouracil, iodourocil, tapazole, et cetera—have been in use since 1943. Of this group, propylthiouracil seems to have the lowest toxicity,[3] and to have the additional advantage of the widest trial. Cope[6] in his review of the subject makes the statement that there is no proved case of hyperthyroidism in which the goiter has not eventually responded with an ultimately normal metabolic rate, provided that the drug is given regularly, persistently and in large enough doses. It has been shown in a well controlled series[15] that with a dose of 250 mg. daily, only one-half of the patients obtained an adequate response. With 300 mg. daily, 95 per cent of the patients were effectively treated, and with 400 mg. all the patients in the group responded. The drug seems to be safe if the patient is warned to report immediately to the physician any rash, fever or sore throat that develops. The average recurrence rate after such therapy has been about 50 per cent. In selected patients, Graves' disease with small to moderate sized glands (not postoperative recurrences)—a maintained remission has been reported in 75 per cent with a follow-up of two years or less.[10] This therapy avoids the disadvantages associated with operation and its complications and with the unknown carcinogenetic possibilities of 1 in 131. It is the only mode of treatment which leaves the patient with an intact thyroid gland.

The disadvantages of the anti-thyroid drugs are: (1) the high recurrence rate which is roughly 50 per cent after only a few years' follow-up; (2) the need for treatment over a period of six to twelve months. Inherent here, of course, is the difficulty of keeping many patients under surveillance for this period of time and, in addition, the necessity for close post-treatment follow-up because of the high recurrence rate.

At the present time it seems to be the consensus that the best method of treatment in most instances remains subtotal thyroidectomy, after adequate preoperative preparation. It possesses all the advantages of the known and sets a good standard for therapeutic results that new therapies must meet. The mortality rate in leading centers with this treatment has dropped to 0.1 per cent. The disadvantages remain: (1) the need for an operation with its attendant discomfort, expense and occasional danger; (2) the occurrence of the two major complications, parathyroid tetany and vocal cord paralysis, both of which continue to appear in about 1 per cent of the patients, even in good hands.

It seems that the anti-thyroid drugs have their greatest field of usefulness as a means of preoperative preparation.[4] Some physicians use them in controlling only those patients who have the disease in severe form preliminary to subtotal thyroidectomy or radio-active iodine administration. Others employ them routinely. With their use the dreaded crisis or thyroid storm has virtually disappeared, as has the need of staged operations for the complicated thyrotoxic patient. Whether the routine or selected use is most efficacious cannot be determined until large series have been observed over a longer period of time. These steps are usually followed:

1. Propylthiouracil, 300-500 mg. per day, in two or three divided doses until the metabolic rate is normal and normal weight approximated. Supportive measures include: high protein, high calorie, high vitamin diet and regulated rest.
2. Iodine is given from the beginning until operation or during the last few weeks prior to operation.
3. The patient is to report fever, rash, or sore throat at once.
4. Propylthiouracil is discontinued one week prior to operation to avoid a possible drug reaction during the immediate postoperative period.
5. Observation with basal metabolic rate and cholesterol determinations for one or two days before operation.
6. Operation only when the patient is perfectly normal.

Toxic Nodular Goiter

Opinions seem practically unanimous that the treatment of choice for toxic nodular goiter is adequate preoperative preparation with one of the anti-thyroid drugs, iodine, diet and rest, followed by subtotal thyroidectomy. This procedure with an operative risk of 0.1 per cent removes the goiter (and allows for its inspection by a pathologist) which statistically has a 1.0 per cent incidence of malignancy. Recurrent hyperthyroidism here is not expected. In the younger patient who refuses operation, control of the disease over a period of one year with one

of the anti-thyroid drugs and iodine would seem best. However, the goiter remains and a recurrence rate of 50 per cent or better can be expected in two years. The patient who is a very poor risk because of associated disease, or the patient who has only a short life expectancy, can be controlled with one of the anti-thyroid drugs and iodine with or without subsequent radio-active iodine. Radio-active iodine, at least at the present time, seems to be contraindicated in the younger patients with toxic nodular goiter because, first, larger amounts of radio-active material are needed to control a given degree of hyperthyroidism in this type of goiter, and thus there is an increased possibility of malignant degeneration due to radiation, and secondly, the patient has a *nodular* goiter with its own hazard of malignant change.

Non-toxic Nodular Goiter

1. Solitary nodules. There seems to be fairly general agreement on a malignancy rate of approximately 20 per cent in this entity.[5,7] Because of this, operative removal is necessary. If malignancy is present, isolateral lobectomy together with a careful search for, and removal of, any suspicious lymph nodes in the drainage area is the only sane approach. If indicated, a radical neck dissection should be carried out. The majority of these malignancies are of low grade so that a thorough procedure initially provides an excellent outlook. The patient should be followed at six-month intervals for at least ten years with the object of surgically removing any further lymph nodes that might appear. Recurrent nodes after twenty years have been reported. We are following one patient with recurrent nodes twenty-two years after her initial surgery. Inadequate primary surgery leads to distant metastasis or, more commonly, local recurrence with or without local invasion and all the difficulties inherent in re-entering the scarred-up site of previous surgery.

2. Lateral aberrant thyroid tumors are now generally recognized as metastases from a primary tumor in the isolateral lobe which necessitates a hemithyroidectomy in addition to the lymph node dissection, even though a palpable tumor in the thyroid is not present.[5,9]

3. Multiple nodules. The incidence of carcinoma in this group varies from a few per cent to as high as 12.8 per cent, depending on whose data you accept.[5,7,11,13] I do not quite know what to make of these statistics. We see a large number of nodular goiters in this area and it is difficult to imagine finding more than 10 per cent of them harboring carcinoma if they were all routinely removed. We have on one hand the large number of multiple nodular goiters seen, and on the other hand the relative rarity of clinical carcinoma of the thyroid developing in such patients. There certainly must be a vast statistical difference between the incidence of carcinoma of the thyroid as judged by microscopic examination and clinical carcinoma of the thyroid as evidenced by extension beyond the confines of the gland or as a cause of death. Admittedly the problem of the pathologist is dfficult for obvious lymph node metastasis may look like normal thyroid tissue and the variety of local changes seen in the thyroid are difficult to assess. The need for correlation of the clinical and pathological evidences is certainly real. It should be remembered that excellent physicians a few years ago reported thirteen out of fourteen parathyroidomata as carcinomatous.[2] This may be true by their histologic criteria, but clinical carcinoma of the parathyroid is exceedingly rare, as judged by recurrence, extension or metastasis in a large series of parathyroid tumors followed over a period of many years.[1] An analogous situation perhaps confronts us in many instances in the thyroid gland. Oschner et al[5] argue logically that they are unable to differentiate carcinoma of the thyroid from benign nodular goiter in at least half of the cases, and that until it is possible to diagnose such carcinoma early by clinical means it must continue to be treated by the best weapon available—"prophylactic thyroidectomy." There is no doubt but that the mortality rate from prophylactic thyroidectomy is a great deal lower than the lowest current figure for the incidence of carcinoma in these glands, as reported frm surgical specimens. However, I continue to wonder about the need for wholesale surgery based alone on the reports from surgical pathology when we see death come to so few people from carcinoma of the thyroid. The argument has been raised that these patients die at home or at some distant center unknown to their physicians. We need better data to prove it.

There is one other attitude that bears on this line of thought. That is the old suggestion that

40 per cent of these goiters become toxic, or that *all* multiple nodular goiters will become toxic if the patient lives long enough. Certainly if one believes this and believes the data on the incidence of carcinoma of the thyroid, there would seem to be very little argument against prophylactic thyroidectomy in any patient with a nodular goiter and a life expectancy of over ten to fifteen years.

Thyroiditis

According to Crile,[8] the three varieties: (1) subacute thyroiditis, (2) struma lymphomatosa (Hashimota) and (3) struma fibrosa (Riedel) are distinct entities and do not progress from one to the other.

Subacute thyroiditis during the acute phase reveals a pseudotuberculous appearance on biopsy similar to that seen in its most chronic form. In any form, operation is not required since the process is self-limited and is said to respond well to doses of x-ray too small to significantly alter thyroid function. In its chronic form and especially when one side is more predominantly involved, confusion with Riedel's struma has occurred. The differentiation is important as Riedel's struma is an irreversible process, will not respond to x-ray, and requires operation for relief of symptoms. The same may be said of carcinoma. If in doubt, biopsy should be carried out before x-ray treatments are started in a patient with clinical diagnosis of subacute thyroiditis, or before operation in suspected Riedel's struma.

Struma lymphomatosa simulates a multi-nodular goiter in a forty to fifty-year-old woman with hypothyroid tendencies. The diagnosis can be established by biopsy with a Silverman needle. Operation is not necessary as the goiter will respond to x-ray therapy and thyroid extract.

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PUBLIC HEALTH SERVICE GRANTS AND FELLOWSHIPS

With publication of a new list, Public Health Service brings to just over $22 million the amount of money it has allocated for medical grants and fellowships within the last twelve months. The most recent tabulation, issued late in October, is for projects approved by the Surgeon General following recommendations made last June by the various National Advisory Councils to the Institutes of Health. In dollar value they amount to just over 13 million. Awards totaling $9.29 million were announced earlier in the year.

In the earlier total were included 143 fellowships, valued at $389,850; fellowships in the October, 1952, totals numbered 540 and were valued at $1,749,248. The latest assistance money was distributed among 1,211 investigators in twenty-one states, the District of Columbia, two territories and seven foreign countries.

National Cancer Institute allocated the largest number of fellowships and grants, 351 worth $2,457,871, while National Heart Institute distributed the most money, $3,464,898 among 338 projects. Totals for other Institutes were as follows: Microbiological, 160 and $1,296,843; Mental Health, 123 and $998,303; Arthritis and Metabolic Disease, 89 and $744,589; Neurological Diseases and Blindness, 91 and $720,910; Dental Research, 37 and $233,728; and non-categorical, 436 and $3,058,683.

—*Capitol Clinic*, Oct. 28, 1952.

NEW DRUGS IN THE TREATMENT OF HYPERTENSION

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THERE ARE several new drugs which may reduce blood pressure in cases of essential hypertension. Some of these drugs are now available for general clinical use. Inasmuch as any of these drugs can produce serious reactions, every physician should become familiar with the accepted proper methods of administering them before he uses them in his practice.

The new drugs which I shall consider are as follows: newer veratrum preparations, particularly protoveratrine; sodium nitroprusside; dihydrogenated ergot alkaloids (hydergine); dibenzyline (688-A); hexamethonium (bistrium, C-6) and pentamethonium (C-5); 1-hydrazinophthalazine (apresoline, C-5968).

Newer Veratrum Preparations

Veratrum viride was one of the earliest drugs to be used in the treatment of hypertension. During the past few years better standardized preparations of veratrum have been available to the physician. This has revived the interest in veratrum in hypertension and toxemias of pregnancy. A number of these preparations are on the market and you are familiar with the use of most of them.

The response of the blood pressure and the patients' reactions to any of the veratrum preparations is variable from patient to patient and even at different times in the same patient on the same dosage. This makes regulation of dosage difficult and requires a carefully worked-out program and continued observation of the patient while taking these drugs.

One of the veratrum preparations most recently under intensive study is protoveratrine, a single-ester alkaloid of Veratrum album, the potency of which is expressed in micrograms. It is available for oral use in tablets, each of which contains 200 or 500 micrograms, or in a solution for intravenous use which contains 100 micrograms per cc.

It was hoped that this preparation would be effective by oral administration in a larger number of patients and that the dose could be more accurately administered than with the older veratrum preparations, thus widening the range between the hypotensive effects and the undesirable side-effects. It would seem from the studies reported that this has not been achieved. Protoveratrine is effective for long-term usage in only about one-third of patients with moderate to severe hypertensive vascular diseases. It has the same disadvantages as the other newer veratrum preparations.

Protoveratrine is useful when given intravenously, subcutaneously, or intramuscularly for the palliation of acute hypertensive crises such as hypertensive encephalopathy with headache, acute pulmonary edema, and toxemia of pregnancy with acute angiospastic episodes. It causes considerable local pain when injected subcutaneously or intramuscularly and if given in this way it should be combined with a local anesthetic, such as procaine hydrochloride.

Meilman has reported that protoveratrine, when administered intravenously, appears to be virtually specific for the headache, nausea, vomiting, insomnia, delirium, and coma of hypertensive encephalopathy, for the congestive failure of acute glomerulonephritis, and for the convulsions of toxemia of pregnancy.

For intravenous administration 1 cc. of the solution (100 micrograms) is diluted to 10 cc. with physiologic saline solution. The injection is given slowly and blood pressure is determined frequently. Administration is stopped when there is a satisfactory decline in blood pressure or relief of the symptoms of the hypertensive crisis. The usual dose administered intravenously is from 50 to 150 micrograms. Meilman advised administering 1.5 to 1.9 micrograms per kilogram of body weight.

Sodium Nitroprusside

According to Page this drug has been studied in the Research Division of the Cleveland Clinic for several years. It produces some interesting effects on the circulation and the blood pressure in animals and in patients with hypertension. In

Read in the Symposium on Therapy at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.
From the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

animals, when given intravenously in very small amounts, it causes a marked fall in blood pressure and vasodilatation in the kidneys. These changes are not dependent on the nervous system.

The immediate effect apparently requires the action of the whole nitroprusside radical. Inasmuch as after a time much of this radical is converted to thiocyanates, the persistent effects may be due to the same effects as those obtained by the administration of thiocyanates. At the Cleveland Clinic the drug has been given orally to a group of patients with hypertension. Its long-term use must be controlled with periodic determinations of the blood cyanates.

The impression of the investigators who have studied this drug is that, although it has some of the properties of the thiocyanates, there is an additional effect which causes it to have a more impressive hypotensive effect than the thiocyanates. Further investigation will be necessary before it can be determined whether or not sodium nitroprusside has any real advantages over the usual method of administering thiocyanates to patients with hypertension.

Dihydrogenated Ergot Alkaloids (Hydergine)

The dihydrogenated ergot alkaloids (dihydroergocornine, dihydroergocristine, dihydroergokryptine) have a central sedative action and produce adrenergic blockage in the periphery. They also act centrally, causing stimulation of the vagal centers which induces bradycardia. This somewhat complicated action is said to cause vascular dilatation with increased peripheral blood pressure and a lowering of systemic blood pressure with bradycardia. The three alkaloids are combined in the preparation hydergine.*

Because of their blood pressure lowering properties the dihydrogenated ergot alkaloids have been used in the treatment of hypertension. Hydergine can be administered intravenously, intramuscularly, or subcutaneously. The unfavorable side-effects are minimal, consisting of nasal stuffiness and occasional nausea and vomiting when given intravenously.

The usual procedure is to give a test dose of 1 to 2 cc. (0.3 mg. to 0.6 mg.) of hydergine intramuscularly after establishing a basal blood pressure level. If there is a moderate but not a severe hypotensive response to this dosage, 1 to 2 cc. is given intramuscularly daily or every other day for a total of about forty injections. If there is no significant decrease in blood pressure with the test dose, the drug is unlikely to be effective in the long-term treatment of that patient.

Significant lowering of blood pressure has been reported to occur in from 25 to 65 per cent of patients with moderate to severe degrees of essential hypertension.[3,4] The development of tolerance has been reported in some cases on prolonged treatment. These drugs would seem most useful in the treatment of hypertensive crises induced by pheochromocytoma or hypertensive encephalopathy rather than in the long-term treatment of essential hypertension.

Dibenzyline (688-A)

Dibenzyline (N-phenoxyisopropyl-N-benzyl-B-chlorethylamine hydrochloride)** is a sympathicolytic and adrenolytic drug which may reduce blood pressure when administered orally or intravenously. It is most effective in reducing the elevated blood pressure resulting from pheochromocytoma, but may reduce blood pressure in cases of essential hypertension. It is less effective when given orally than when given intravenously. Bello and Soloff, in a small series of patients, found that dibenzyline, when administered orally, failed to reduce blood pressure in the hypertensive subject or to give any evidence of absorption. Allen and his associates also found that the oral administration of dibenzyline produced a much less dramatic reduction than intravenous injection.

Dibenzyline may be given slowly intravenously when diluted in 500 cc. of a 5 per cent solution of dextrose. The optimal total dosage is approximately 1 mg. for each kilogram of body weight. The reduction in blood pressure lasts two to nineteen hours. The intravenous administration of the drug is probably of less usefulness than the intravenous administration of protoveratrine in treating hypertensive crises, as untoward reactions frequently occur when dibenzyline is administered intravenously. The oral administration of the drug for long-term use in essential hypertension requires further study.

*Manufactured by Sandoz Pharmaceuticals, Division of Sandoz Chemical Works, Inc., New York, New York.

**Manufactured by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

Hexamethonium (Bistrium,* C-6); Pentamethonium (C-5)

Hexamethonium, a derivative of the polymethyline ammonium compounds, inhibits the action of the autonomic nervous system by blocking the impulses at the ganglia. The effects are similar to those of tetraethylammonium chloride, but are of much longer duration. Pentamethonium is similar in action, but has been less extensively used than hexamethonium. It is usually administered in the bromide compound and may be given orally, subcutaneously, or intravenously. The effect of hexamethonium is more prolonged but probably not greater in degree if renal insufficiency is present, unless there has also been a lowering of sodium in the serum due either to the disease or to the intake of a diet which is low in sodium content. It is rarely necessary to administer hexamethonium intravenously, and if given in this way the initial dosage should be very small, probably not more than 1 mg. or less, as very serious hypotensive reactions may occur. The oral administration of the drug occasionally causes serious complications, and if it is administered orally, the patient should be kept under close supervision.

The subcutaneous dose of the drug is 15 to 200 mg. This dose should be administered every six to twelve hours, depending on the response of the blood pressure. Larger doses must be used when the drug is administered orally than when it is injected subcutaneously. It is agreed that the oral administration of hexamethonium is less effective in reducing the blood pressure than is the administration by subcutaneous injection.

The undesirable reactions which may result from injections of hexamethonium are severe hypotension, marked orthostatic hypotension, constipation, paralytic ileus, and difficulty in micturition. Severe hypotension is evidence of overdosage and should be treated by placing the patient in the recumbent position and by elevating the foot of the bed. It may be necessary to administer 2 to 5 mg. of phenylephrine hydrochloride (neosynephrine) intravenously if severe hypotension persists.

The complications, constipation, paralytic ileus, and urinary retention, may be prevented by the sublingual administration of 5 to 20 mg. of urecholine chloride (bethanechol chloride).

*Manufactured by E. R. Squibb & Sons, New York, New York.

1-Hydrazinophthalazine

1-Hydrazinophthalazine was designated originally as C-5968,‡ and is now supplied as apresoline. It appears to reduce blood pressure by its action on the midbrain or hindbrain, and according to Schroeder[7] inactivates many pressor substances in the blood, such as pherentasin, hypertensin, and others. The dose varies from 50 to 150 mg., which should be administered orally three to five times daily.

Undesirable side-effects are headache, tachycardia, and severe orthostatic hypotension. Nausea and vomiting, paresthesias in the extremities, nervous tension, and mental depression may occur occasionally. The milder side-effects usually subside within three or four hours and require no treatment. Headache, if severe and prolonged, may be controlled by the administration of dimethyl-hydrinate (dramamine), or aspirin, and can be prevented by the prior administration of hexamethonium bromide.

1-Hydrazinophthalazine administered alone has been found to be an antihypertensive agent of only moderate potency. A significant reduction in blood pressure occurs in about 70 per cent of cases, but the blood pressure almost never is maintained at or near a normal level.

Administration of 1-Hydrazinophthalazine With Hexamethonium Bromide

Because of the reported difference in the mode of action of the two drugs, one acting predominantly peripherally and the other centrally or by inactivating pressor substances in the blood, it was logical to try a combination of these drugs. Some investigators believe that the most effective method now available for treating essential hypertension is by administering 1-Hydrazinophthalazine and hexamethonium bromide together or on an alternating dosage program. Others do not believe these drugs have a synergistic action.

Schroeder[7,8] has reported that this combined therapy resulted in complete control of the hypertension in all cases of benign hypertension and in all but two of thirty cases in the malignant stage without renal insufficiency. He had observed that too quick withdrawal of the drugs was associated with serious reactions and that these reactions had resulted in death within a few days or weeks after withdrawal in six patients. Schroeder stated

‡Manufactured by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

that no tolerance to the drugs developed in patients after normal blood pressure had been established, or if the patient had been taking the drugs satisfactorily for more than a month. In the malignant stage, in which normal blood pressure levels are not usually attained with the drugs, tolerance may develop in the early weeks of treatment.

These two drugs have been used in a clinical study at the Mayo Clinic by Drs. Allen, Barker, Kvale, Shick, Estes and myself for the past eight months. We have obtained information sufficient to enable us to form an opinion as to the value of these drugs in the treatment of severe essential hypertension over a period of a few weeks or months, but not for longer periods.

Patients to whom these drugs are to be administered must be hospitalized for a minimal period of three weeks for preliminary observation and careful adjustment of dosage. We have treated patients with group three and group four essential hypertension less than fifty years of age, or patients with group two essential hypertension whose blood pressures are more than 200 mm. of mercury systolic and 120 diastolic. Patients with severe renal insufficiency have not been given these drugs.

The period of observation was begun with a pretreatment control period of from one to three days without the use of sedatives or other drugs. Treatment with hexamethonium bromide was started with a test dose of 15 mg. administered subcutaneously. The blood pressure of the patient was taken in the supine, seated, and erect positions several times during the first hour after the drug was administered, and any untoward reactions, especially marked orthostatic hypotension, were noted. If orthostatic hypotension was not severe, 15 mg. of hexamethonium bromide was given subcutaneously every twelve hours. The blood pressure was always taken before the next injection was given. If the blood pressure was lower than 130 mm. of mercury systolic, the next dose was omitted. If the blood pressure was not lowered, the dosage of hexamethonium bromide could be increased gradually to a total of 100 mg. over a period of two or three weeks.

Administration of 1-Hydrazinophthalazine, beginning with doses of 25 mg., was started six hours after the last injection of hexamethonium bromide. The initial dose should be no more than 25 mg. The dose was gradually increased up to a maximum of 200 mg. over a period of two or three weeks.

Most of our study was carried out by using the drugs concurrently. Hexamethonium bromide has been given subcutaneously at 6 a.m. and 6 p.m., and 1-Hydrazinophthalazine at noon and at midnight. The dosage of both drugs has been small at the beginning and has been gradually increased, depending on the side-reactions that occurred and on the patient's tolerance to the drug. Schroeder[8] has emphasized that to avoid the development of tolerance to the oral method of administration it is necessary to give the patient gradually increasing doses every day or every few days until the maximal effective dosage has been reached. We do not know whether or not such frequent increase in dosage is necessary if hexamethonium bromide is administered parenterally.

In general, we have been encouraged by the use of these drugs, particularly hexamethonium bromide, in the treatment of selected cases of essential hypertension. Subcutaneous administration of hexamethonium bromide produces a lowering of blood pressure in most cases and in many it produces a marked orthostatic hypotension with all the unpleasant secondary effects. These effects usually persist for three or four hours and usually become less noticeable as the injections are continued, even though the dosage is increased. We have observed the development of tolerance to the combined program in several patients within the first few weeks of treatment. 1-Hydrazinophthalazine seems to be less effective than hexamethonium bromide in the dosage we have employed. In many patients a high fixed elevation of blood pressure has become more labile in the lower ranges while they were taking the two drugs. In some cases the hypertension may be said to have been satisfactorily controlled on this program of treatment during the limited time of our observation.

Patients may be instructed to administer the medication to themselves and, unless they are under the closest observation of a physician, to take their own blood pressure so that they can properly regulate their dosage of medication.

One of the disadvantages of this program for the long-term treatment of hypertension is that it cannot be carried out satisfactorily unless the patient is intelligent and co-operative and can adequately control the administration of the drugs to himself.

(Continued on Page 1051)

TREATMENT OF THE CONVULSIVE DISORDERS

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THE PRIMARY objective of this paper is to stress the importance of the physician's responsibility in the treatment of the convulsive patient and to enable the convulsive patient to live the fullest, happiest life possible. Concomitantly it is often necessary to reassure and educate both the patient and near relatives. Each "epileptic" represents a challenge to the practitioner not only to completely control the seizures but also to achieve adequate social and economic adjustment. Successful medical management must include personality adjustment where necessary and an integrative rehabilitation program. The word "epilepsy" to the layman's mind continues to precipitate erroneous and alarming ideas, reminiscent of folklore. A convulsion is so dramatic in its manifestations that it is little wonder that the ancients conceived an individual so afflicted to be inhabited by the devil. Descriptions of the "fallen evil" later modified to "falling sickness" are found in writings of the ancient Egyptians, Arabians, and Hebrews. Thomas Willis[1] in the Eighteenth Century likened the convulsive attack to the explosion of a gunpowder charge and stated that the final cause is chemical in origin, a conclusion upheld by present-day investigators.

The modern era for the investigation and research in convulsive disorders to great extent followed the introduction of the electroencephalogram by Hans Berger in 1929. The development of the EEG has revealed differences between epileptics and normals, has shown what is taking place in the brain during the seizure and between seizures, and has uncovered new evidence about causal lesions. Treatment of the convulsive disorders has paralleled the advance of electroencephalography. The instrument has opened up new avenues for investigation and provided the spark for stimulating research. The EEG, however, does not tell us much about normal cerebral physiology, and certainly does not tell us why some individuals with brain trauma, cerebral neoplasm, et cetera have a convulsion and others do not; nor why a certain percentage (10 to 15 per cent) of epileptic patients will have a normal interim EEG record; nor why some patients become clinically seizure-free whereas the EEG tracing may become more abnormal. Nevertheless, the brain-wave apparatus has given to the clinician tremendous information to aid in proper diagnosis, the type of seizure discharge, and thus tend to indicate the proper anticonvulsant medication. The observations made with the EEG have confirmed many of the deductions of the pioneer neurologists (Jackson,[5] Gowers,[2] and others) and have further extended the knowledge of the spread of seizure discharge over the brain. Present-day investigation is also concerned with the chemical alterations, as abnormal concentrations of acetylcholine, that take place in the epileptogenic focus, and the mechanisms by which the various anticonvulsants are effective.

Inasmuch as we do not fully comprehend the fundamental mechanisms underlying the convulsive states, no wholly satisfactory definition can be given. Most definitions are purely descriptive. Lennox (1944) defines it in a comprehensive fashion: "epilepsy is a recurrent disturbance in the chemico-electrical activity of the brain which manifests itself in a symptom complex of which impairment of consciousness, perturbation of the autonomic nervous system, convulsive movements, or psychic disturbances are the essential components."[8]

Epilepsy presents a social and economic problem of considerable magnitude, for its incidence is surprisingly high. There are approximately 800,000 people in the U.S.A. with a convulsive disorder, an incidence of one in 200. This is a conservative estimate, as in many cases seizures are overlooked, concealed, or incorporated with other diagnoses. The number of veterans[10] afflicted with epilepsy is approximately 50,000,

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Read in the Symposium on Therapy at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

and it is expected that half of the 15,000 military men who survived penetrating brain injuries will develop post-traumatic epilepsy. The other social aspect of the problem of epilepsy is the hereditary element. Lennox[8] states that 17 per cent of the relatives of an epileptic patient had convulsions whereas the incidence of convulsions in normal families is 3.4 per cent. Lennox, Gibbs, and Gibbs[9] (1940) found that in a group of epileptics both parents had an abnormal EEG record in 28 per cent and with at least one parent in 94 per cent. These authors imply that the cortical dysrhythmia is inheritable, which may predispose the offspring to epilepsy. Williams[16] (1950) elaborates the hypothesis and believes that in addition to the tendency to epilepsy there must be another factor, that is the failure to prevent the spread of convulsive process. This limiting factor may be all important in preventing the clinical attack or in the alteration of the attack, thus giving use to the differences witnessed in the sub-types of the condition.

The practical aspect of the genetic factor presents itself when an epileptic patient asks for advice about having children. Barring all complications the incidence of having an epileptic child, wherein one parent only is a convulsive, is not much greater than the normal occurring incidence for epilepsy.

It is to be recalled that epilepsy is a syndrome whose presenting symptoms may vary from mild psychical states to severe status epilepticus. Every individual who has a convulsive attack warrants a complete medical and neurologic workup. A searching attack to uncover the etiology of the seizure discharge is of utmost importance in the proper management of the patient. If this be accomplished the diagnosis of so-called idiopathic epilepsy (essential, genuine) will not invariably be made, and the incidence of acquired (symptomatic) epilepsy will be surprisingly high. Nevertheless, it is true there will remain a large group of patients with no demonstrable organic pathology either by examination or by historical inference. The etiology of the epileptic patients seen by the individual practitioner to a large extent depends upon the physician's type of practice. Thus the neurologist and neurosurgeon will have a high incidence of brain tumors amongst their epileptics, the pediatricians a high incidence of brain trauma at birth, the state hospital superintendent a high incidence of congenital abnormalities and profound brain trauma, and the general practitioner more apt to see the normal ratio of genetic and sub-varieties of acquired epilepsy.

In addition to subdividing the convulsive disorders into the genuine (essential) or acquired etiologic groups, these disorders for purposes of diagnosis and treatment are classified according to the clinical type of seizure manifested by the epileptic. The vast majority of all seizures can be classified in one of six main groups. The classification is based primarily on the physical appearance of the patient during the seizure, but also in part on the EEG tracing. An observed seizure may be atypical or a mixture of two types, or may defy classification.

Type of Seizures

1. Jacksonian Motor Seizures, and Focal Motor Seizures.
2. Somatic Sensory Seizures.
3. Grand Mal (Generalized) Seizures.
4. Psychomotor or Psychic Equivalents.
5. Petit Mal Triad or Pyknolepsy.
6. Autonomic (Diencephalic) Seizures.

Anticonvulsive Therapy

As is true with all diseases the primary objectives of treatment are removal of the cause or causes, alleviate the symptoms, and prevent sequelae. Treatment falls into several main groups: (1) general; (2) psychological; (3) drugs; (4) dietary; (5) surgical.

General.—Experience has taught us that patients are less likely to have convulsions if they lead a well-balanced, equitable life. The epileptic should be directed to lead as normal an existence compatible with his type of seizures. Only such restrictions should be made that are necessary to safeguard the patient and the public. In this regard epileptic patients should not operate heavy machinery or drive automobiles until their seizures have been under complete control for at least several years. Every attempt should be made to correct incidental physical abnormalities and to keep the patient in good sound physical state. All types of alcoholic beverages tend to precipitate seizures and should therefore be absolutely forbidden. The only possible exception may be in the case of an elderly individual whose seizures are secondary to cerebral arteriosclerosis, and wherein an occasional drink increases cerebral

circulation. The intake of non-alcoholic beverages by the young patients especially bears watching during the hot weather.

Psychological.—Proper mental hygiene is exceedingly important. Patients should not be shrugged off by merely administration of drugs. Most patients suffer more from the fear of seizures and social implications than from the seizure itself. The social stigma is still present even in this period of mental health enlightenment. This attitude is fostered by concealment by the patient's relatives, and the prevalent tendency that employers and educators have of getting rid of the epileptic from work and school. A great deal of restriction is introduced under the guise of safety. Patients and their families need to be protected from discouragement and this element of horror. Even though the physician cannot attain complete relief of seizures in every patient, he can inject and cultivate hope and morale in many. All questions relating to intellect, sanity, heredity, marriage, et cetera should be frankly discussed. The various myths and folklore pertaining to epilepsy should be exploded. It must be emphasized that the anticonvulsant drugs employed are neither "dope" nor habit forming. Clinical evidence indicates that in a number of patients anxiety, tension, fear, and the like may actually precipitate or increase the number of seizures. Important as psychological health is in the therapy of the epileptic it in itself cannot adequately control the seizure discharge. From the therapeutic point of view the greatest advances in therapy have come about through the introduction of new anticonvulsant drugs.

Pharmacotherapy of Epilepsy.—The recent increase in the number of anticonvulsants available has to a certain extent complicated the task of choosing the proper drug for the individual patient. A drug that may be effective for one type of seizure may be harmful for another; that is, a single drug may control petit mal and accentuate grand mal. The selection of medication depends primarily upon the type of seizure. Much time and grief can be eliminated by choosing the drug most likely to succeed.

Approximately 100 years have passed since bromides were first used in the treatment of seizures. Credit belongs to Sir Charles Locock,[11] who reported the use of bromides in 1857. The drug was introduced to treat onanism, which supposedly was the cause of the seizures. Considering the inadequacy of previous medications, the introduction of bromides was a tremendous therapeutic advance and received with ready acceptance and acclaim. Enthusiasm for the newer drugs has relegated and threatened to displace the bromides altogether. Nevertheless various studies (Pollock[14]) substantiate the effectiveness of the bromides when administered skillfully.

The next important milestone in the development of pharmacotherapy was the use of phenobarbital in 1912 by Hauptman.[4] However, it was not put to general use until after World War I. The first report in the American literature was that of Grinker's[3] in 1920, following which the drug received wide acceptance and innumerable articles were published heralding this new anticonvulsant.

Up until the mid 1930's it was the opinion that effectiveness of bromides and barbiturates was secondary to their sedative powers. Merritt and Putnam[15] reasoned that the protection offered by these drugs might be specifically anticonvulsant rather than hypnotic and in 1937 introduced Dilantin after an exhaustive study of approximately fifty various compounds. Dilantin (diphenylhydantoin sodium) was the least sedative and best anticonvulsant of the drugs tested. In June, 1938, before the AMA meeting in San Francisco, Merritt and Putnam[12] reviewed their clinical experience with Dilantin. In the decade following numerous other hydantoins were investigated and offered for clinical use. The most commonly used in addition to Dilantin are Mesantoin (methyl phenylethyl hydantoin) and Thiantoin (phenyl thienyl hydantoinate).

The use of the hydantoins together with barbiturates and bromides gave to the clinician an excellent combination for treatment of the major (grand mal) attack, but was disappointing in treatment of petit mal triad. Thus the search continued and in 1945 Lennox[7] reported on the effectiveness of Tridione (trimethyloxazolidine dione), and later Paradione (dimethylethyloxazolidine dione). Other new anticonvulsants have been available to the clinician, including the other hydantoins and recently Phenurone (phenacetyl urea).

We are still looking for the ideal anticonvulsant, one which should offer complete control against seizures, be equally effective against all

types of seizures, and be free of side-effects. Williams[16] believes that the sedative anticonvulsants (barbiturates) protect the brain from the epileptogenic focus whereas the hydantoins directly inhibit the epileptic process without depressing the remainder of the cerebral cortex.

The chief pitfall in the treatment of convulsive disorders is failure to use the correct medication, or the failure to use a sufficient amount of the medication or medications.

Specific Drugs

Phenylethylbarbituric acid (Phenobarbital).—Phenobarbital is a sedative, and drowsiness frequently limits the amount that can be given. Individual susceptibility varies widely. Those who are allergic to the drug will develop a rash usually within two to three weeks. Overdosage results in the common barbiturate toxic symptoms, viz: ataxia, slurred speech, mental cloudiness and in the extreme case, coma. Phenobarbital is available in white tablets containing ¼, ½ and 1½ gr. It also may be dispensed as an elixir, ¼ gr. per teaspoonful, or given parenterally in the soluble sodium salt. It is extremely useful alone or in combination with other anticonvulsants in the treatment of grand mal, Jacksonian, and focal seizures. It is less effective in the treatment of psychomotor attacks and petit mal triad. Parenterally it is excellent for control of status epilepticus. It is excreted slowly, so that it need be given only once or twice per day, and usually given at bedtime to prevent drowsiness. Seldom is the total daily amount pursued beyond 3 to 4½ gr.

Diphenylhydantoin sodium (phenytoin sodium—Dilantin).—This is the drug of choice for the treatment of all major convulsions (grand mal), Jacksonian, and focal seizures, and the drug to be first tried in psychomotor seizures. It possesses effective anticonvulsant properties with little hypnotic effect. However, its administration requires careful supervision as the dose required to produce therapeutic effect may approach that at which toxic symptoms appear. Approximately 10-20 per cent of patients will have moderate reversible toxic reactions, of which are giddiness, inco-ordination, tremor, double vision, nystagmus, skin rash, gastric distress, and hypertrophy of the gums. Rarely an occasional patient may experience psychotic-like symptoms. These symptoms may be overcome by temporary reduction or withdrawal and then gradual readministration.

The drug is supplied in sealed capsules as follows: ½ gr., 1½ gr., 1½ gr. with ¼ gr. Phenobarbital, 1½ gr. Dilantin in oil, and 1½ gr. enteric coated capsules. For adults the usual dosage is one capsule (gr. 1½) three times a day, with each meal. If seizures continue an additional capsule at bedtime and if necessary increase to five to six capsules per day until seizures are controlled or unpleasant side-effects appear. If uncontrolled on four and five 1½ gr. capsules or they produce unpleasant reactions, compromise may be reached by taking four and five capsules on alternate days. Continuance of seizures on maximal tolerated dosage requires the addition of one of the other hydantoins or barbiturates.

For those individuals who complain of gastric distress while taking Dilantin, Dilantin in oil is recommended. An enteric coated capsule may be prescribed with plain Dilantin capsule at bedtime to provide for "around the clock" regime. For young children one-half the adult dosage is prescribed with gradual increase as needed.

With long continued use of Dilantin, most patients retain their initial improvement; however, an occasional patient after a long period of control may experience a recurrence of seizures. According to Williams,[6] when a patient taking hydantoins has a convulsion, he does so in an unprotected cerebrum which responds maximally, supporting the theory that the various anticonvulsants available operate in a dual fashion: (1) by reduction of the focus of irritability and (2) increasing the convulsive threshold of the remainder of the brain.

Methylethylphenyl barbituric acid (mephobarbital, Mebaral).—The sedative effect of Mebaral grain for grain is less than for Phenobarbital, hence larger amounts of the drug can be used without the production of mental clouding. It is frequently used in combination with the hydantoins and diones. It is supplied in ½ gr., 1½ gr. and 3 gr. white tablets. For adults starting dosage is 1½ to 3 gr. tablet three times a day.

Methylphenylethyl hydantoin (Mesantoin).—This drug is closely related to Dilantin and may be substituted for it or used in conjunction with

it and the barbiturates. It is of minimal effect in the petit mal triad. Its superiority over Dilantin cannot be predicted. Even though Mesantoin can be given in much higher dosages than Dilantin, produces little or no ataxia, gum hypertrophy, gastric irritation, or hirsutism, it has the serious drawback that in the occasional patient it produces bone marrow depression with resultant blood dyscrasia and possible death. The less disturbing toxic or sensitivity symptoms include morbilliform rash with fever and itching, lymphadenopathy, and bleeding from the mucous membrane. Mesantoin is available in 1½ gr. pink tablets and in combination with ⅓ gr. Phenobarbital (Hydantal). Dosage is similar to Dilantin.

Sodium phenylthienyl hydantoin (Thiantoin sodium).—It is closely related chemically to Dilantin and has similar therapeutic and side effects. Although the drug has been available for over eight years reports in the literature are few. Peterman's reports[13] are favorable. There is no indication that Thiantoin precipitates or accentuates other types of seizures. It is available in 2 and 4 gr. capsules and in a lime colored suspension, 2 gr. per dram. The usual adult dose is 2 gr. three to four times a day.

Bromides.—The bromides, the original effective anticonvulsant, have been excelled by those previously mentioned, but should not be forgotten when the occasional patient fails to respond to the newer drugs. The side effects which limit the dosage are acne-like skin eruptions, mental apathy, and occasionally psychotic behavior. Although the bromides unlike the other antiepileptics can be measured in body fluids, the serum concentration does not parallel the clinical effectiveness. Bromides are available in 10 gr. tablet form, powder or solution. The adult dosage varies from 2.0 to 4.0 gm. per day.

Trimethyloazolidine dione (Tridione).—This is the drug of choice in the treatment of the petit mal triad and occasionally useful in psychomotor attacks when used with the hydantoins and barbiturates. Tridione unfortunately may precipitate or increase the number of grand mal attacks while controlling petit mal and should therefore seldom be used alone and should always be combined with the other anticonvulsants in an individual who suffers from both major and minor attacks. The minor side reactions, which may require temporary cessation, include gastric distress, morbilliform rash, somnolence, irrritability, hemeralopia, and hiccoughs. The potentially most serious complications are bone marrow depression, nephrosis, and exfoliative dermatitis. A number of fatalities have been recorded. Tridione is dispensed in capsules containing 5 gr. or as a peppermint flavored elixir 2½ gr. per dram. The adult dosage varies from 15 to 30 gr. per day, and for young children initial dosage is 7½ to 10 gr. per day.

Dimethylethyloxazolidine dione (Paradione).—It is an analogue of Tridione, similar in action, but although less apt to be toxic than Tridione, is less effective in the treatment of the petit mal triad. It is dispensed in two sizes, gr. 5 and gr. 2½. Dosage is similar to Tridione.

Phenacetylurea (Phenurone).—After four years' trial the drug is now available on the market. It is recommended in stubborn cases of epilepsy, chiefly psychomotor seizures, when the other anticonvulsants have failed. It should be used only with the full realization that it is potentially dangerous. One of the most frequent side reactions seen is a personality change, varying from mild depression to frank psychosis. Other reactions include nausea and vomiting, anorexia, headache, drowsiness, weakness, et cetera. The alarming toxic reactions include bone marrow depression and liver damage. Several deaths have been reported. Phenurone is supplied in 0.5 gm. bisected tablets. It is reported that side reactions are less apt to develop if the drug is gradually increased. Starting adult dosage is one tablet (0.5 gm.) three times a day with meals. If no untoward effects after one week, an additional tablet may be taken on arising and later on a tablet at bedtime. An average dosage of five to six tablets per day is the most adequate.

Accessory Drugs.—An essential amino acid, glutamic acid, available in 0.5 gm. tablets, has occasionally been used with some success in the treatment of minor attacks. Theoretically its effectiveness results from reduction of cerebral alkalinity. The enthusiasm for improving mental retardation and control of petit mal attacks has not been upheld by recent investigators. The

amphetamines (Benzedrine, Dexedrine) are useful in counteracting the sedative action of large dosages of the anticonvulsants and are useful in controlling nocturnal seizures. Presumably this latter effect is produced by alteration of the sleep mechanism, and thereby resulting in a lessened depth of sleep.

Summary of Drug Therapy

For the control of motor seizures (generalized, Jacksonian, and focal), the hydantoins and barbiturates, alone or in combination, are the most efficacious. These drugs in various combinations should be tried first for control of the psychomotor seizures, and if unsuccessful, a switch to Phenurone, singly or in combination. For the petit mal triad the diones are most specific. When more than one type of seizure is present in a patient or a single durg is apt to percipitate another variety, combinations are mandatory. The drug least apt to produce side reactions is to be tried first. Frequently the "trial and error" method is necessary to determine the correct medication and dosage. Nevertheless the use of electroencephalography frequently indicates the specific medication or medications. The dosage must be individualized and must be given in adequate amount.

The bromides, Dilantin, Mebaral, and Phenobarbital are safe drugs. Fatal reactions are virtually unknown when used in therapeutic range. About 10 per cent of patients have moderate, reversible side reactions and less than 1 per cent have severe toxic reactions. About 35 per cent of patients will have moderately severe but reversible side reactions with Mesantoin, Phenurone, Tridione, and Paradione, and dangerous toxic reactions in 1-2 per cent. Phenurone is known to produce liver damage. Serious reactions to Tridione, Paradione, and Mesantoin are pancytopenia and exfoliative dermatitis, and also the diones cause nephrosis. About thirty deaths have been reported in the last six years.

A new drug that is potentially dangerous should be given only if the physician is certain that the patient will follow instructions, keep appointments for routine checkups, including urinalysis and hematologic studies. Hematologic changes occur in stages: (1) modified normal response, (2) then controlled neutropenia, and (3) finally pancytopenia. Peripheral blood work does not necessarily parallel the activity of the bone marrow, as the latter may be damaged without immediate detection in the circulating blood. A white blood count below 2,000 cells is an absolute indication for withdrawal of the offending anticonvulsant.

Dietary Therapy.—Brain metabolism may be altered by the ingestion of various foods. Repeated clinical studies have demonstrated the beneficial effect of ketosis. Over thirty years ago an osteopathic practitioner advertised to the effect that abstinence of food was of benefit in control of convulsions. Later in a number of clinical laboratories studies in blood chemistry and acid-base balance were conducted. Starvation gave way to production of ketosis by means of a diet rich in fat and poor in carbohydrates. This ketogenic diet was most effective in the treatment of children and more specifically the petit mal attacks of children. Because the diets are difficult to prepare, expensive, and unappetizing to the patient they are seldom prescribed and dietary treatment has given way to the newer anticonvulsants.

Surgical Therapy.—It is obvious that if the patient's seizures are secondary to a brain tumor or other type of expanding intracranial lesion (hematoma, granuloma, abscess) that craniotomy is indicated; and it is equally understandable that the brain operation does not necessarily free the patient from seizures. After operative intervention medical therapy is to be maintained for a minimum of two years.

Surgical removal of epileptogenic foci, including post-traumatic and post-infectious scars has become increasingly popular with the advent of electrocorticography. Temporal lobectomy in the treatment of intractable psychomotor epilepsy and hemispherectomy of a severely injured cerebral hemisphere, peppered with epileptogenic foci, have shown promise. These surgical procedures for removal of unstable brain foci are justified when medical therapy fails. After cortical resection of these foci anticonvulsants must be continued for several years for safe measure. Surgical therapy does not imply discontinuance of pharmacotherapy, it renders the latter more successful.

(Continued on Page 1041)

DRUG THERAPY IN PARKINSONISM

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THE TREATMENT of a patient with parkinsonism is a combination of intelligent use of drugs, emotional readjustment and exercise. A great number of drugs have been used at one time or another. Most of these medications are now only of historical interest and are documented in a number of excellent reviews.[22,23,24,41] However, definite improvement in the clinical picture has been produced by some medications, and encouraged by this, investigators are still in search of the ideal drug for the treatment of parkinsonism. In view of the large numbers of new drugs introduced in recent years in therapy of this disease, a review of this phase of therapy seems timely. The medications currently in use or under investigation will be considered. The author's comments on the use of these medications are based on the experience of treating one hundred patients with parkinsonism over a three-year period at the parkinsonism clinic of the University Hospitals.

1. *Belladonna Derivatives.*—Excellent reviews on the belladonna drugs are available.[5,16,28,41] The belladonna drugs are widely distributed in nature, especially in the Solanaceae plants. Galenecal preparations of belladonna have been employed in medicine for many centuries and were known to the ancient Hindus. The professional poisoners of the middle ages often employed the deadly nightshade plant to produce a type of intoxication which was often prolonged and obscure. This prompted Linné to name this shrub Atropa belladonna, after Atropos, the oldest of the three fates who severs the thread of life. The word "belladonna" itself is a reminder of the antiquity of these medicines in that it signifies "beautiful lady," the women of long ago being wont to instill a decoction of belladonna in their eyes to produce dilated pupils, a sign of comeliness. In the treatment of parkinsonism, drugs of the belladonna group have been used since Ynauch in 1882 advocated the use of hyoscine. After that date, various alkaloids of belladonna, including atropine, hyoscyamine and scopolamine have been used extensively.

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In 1926, Raeff,[41] a plant collector, used extracts of Bulgarian belladonna root to treat parkinsonism. This form of therapy was taken up and extended by Panegrossi,[41] who designated it the Bulgarian treatment. It was soon proved, however, that the Bulgarian belladonna root had no properties which made it superior as a therapeutic agent to the belladonna grown in other countries. Vollmer[39] considered that extracts of belladonna were too inconstant in the concentration of alkaloids and recommended the use of synthetic compounds, containing known concentrations of the various alkaloids. Extensive comparative studies[5,7] have shown that the alkaloids, root extracts and synthetic compounds have similar action and owe their activity to the alkaloids they contain. No one preparation is clearly superior to others. It is necessary to try the various drugs to find the one which is best for the individual patient. A change in medication may be necessary at a later date, and it is frequently necessary to shift from one drug to another for the maximum therapeutic benefit.[4,42]

The active alkaloids of the belladonna group used in the treatment of parkinsonism are atropine, scopolamine (hyoscine) and hyoscyamine. Atropine and hyoscine are used independently in the treatment of parkinsonism. Atropine[7] is administered in a 0.5 per cent solution commencing with 1 drop t.i.d and increasing to 10 drops t.i.d. Hyoscine is administered as hyoscine hydrobromide in tablets of gr. 1/100 and gr. 1/150. The amount of hyoscine hydrobromide given is that which produces the maximum benefit for the patient.

Tincture of stramonium contains atropine and hyoscyamine. The mode of administration of this drug recommended by Doshay[7] is to start with 20 drops t.i.d and slowly build up to 60 drops t.i.d.

The remainder of the drugs of the belladonna group, bellabulgara, rabellon and vinobel, are compounds, which contain varying proportions of atropine, scopolamine and hyoscyamine. Bellabulgara is a Lederle product. Each tablet of bellabulgara contains .4 mgm. of the total alkaloid of belladonna. Rabellon is a Sharp and Dohme

TABLE I. RABELLON SCHEDULE

Rabellon Tablets—.5 mg. each

Days	*A.M.*	*Noon*	*Bedtime*
1	¼	¼	¼
2	½	½	½
3	½	½	¾
4	¾	¾	¾
5	¾	¾	1
6	1	¾	1
7	1	1	1
8	1	1	1¼
9	1¼	1	1¼
10	1¼	1¼	1¼
11	1¼	1¼	1½
12	1½	1¼	1½
13	1½	1½	1½
14	1½	1½	1¾
15	1¾	1½	1¾
16	1¾	1¾	1¾
17	1¾	1¾	2
18	1¾	2	2
19	2	2	2

Increase thereafter by ¼ tablet daily. If any toxic symptoms occur, such as *excessive* dryness of mouth, dizziness or blurring of vision, return to dosage of previous day for one week and then attempt to increase again. An attempt should be made to maintain maximum dosage without untoward symptoms.

product and comes in .5 mgm. tablets. Each tablet contains .45 mgm. of hyoscyamine, .037 mgm. of atropine and .012 mgm. of scopolamine. Numerous publications[11,14,15,25,38,39,40] confirm the beneficial effect of this medication. Vinobel is a Merrill product. The tablets are of two sizes, .4 mgm. (red in color) and .8 mgm. tablet (orange in color). Numerous publications[7,25] confirm its therapeutic effect.

The toxic symptoms encountered in the use of drugs of the belladonna series are dryness of the mouth; urinary retention; visual blurring; gastrointestinal symptoms such as nausea, diarrhea and constipation; central nervous system symptoms such as headache, dizziness, and in some instances confusion, delirium and hallucinations.

Comment.—Rabellon, vinobel, bellabulgara and to a lesser extent hyoscine and atropine are the drugs of this group which are being used in the clinic. Atropine is particularly useful where salivation is a difficult symptom to control and the addition of atropine sometimes produces a gratifying amelioration of this troublesome symptom. The mode of administration of the drugs of belladonna series is to determine initially the maximum dosage of the drugs that the patient can tolerate and then to determine the minimum dosage which produces the maximum therapeutic effect. This is the maintenance dose of the drug. Table I illustrates the scheme which is used in the administration of rabellon. A similar schedule is followed when the other drugs are prescribed. It should be noticed that the maximum dose of the drug is given before retiring so that if toxic symptoms are encountered, they will occur while the patient is asleep and thus cause a minimum of discomfort.

2. *Dihydro-beta-erythroidine.*—The clinical use of this drug was reported by Shapiro and Baker[33] in 1950. The drug is an alkaloid and the usual dosage is four of the 50 mgm. tablets per day. This drug is used as an adjunct to the atropine derivatives. It is indicated where rigidity is a feature. It has little effect on tremor or upon the oculogyric crises. The toxic symptoms are usually transient and consist of gastrointestinal manifestation, visual disturbance and some dizziness.

Comment.—Further experience with this drug substantiates the findings as reported in 1950.

3. *Parpanit.*—In 1946 Grunthal[17] reported on the use of "parpanit," an antispasmodic related to "trasentine," in a number of extra-pyramidal disorders and found it more efficient and less toxic than the atropine-like substances. Hartmann[18,19] confirmed these observations in 1946 and 1947, finding parpanit far more efficient in Parkinson's disease than the atropine-like drugs and reported briefly on its use in about forty patients. Schwab and Leigh[30] studied its effects in fifty patients over a period of three months, and basing their views largely on the patient's ability to carry out the ordinary "chores of life," they considered that parpanit was more efficacious than the solanaceous drugs in 62 per cent of the cases, that it had an equal effect in 22 per cent, and that in 16 per cent the effect was not so good. Their dosage ranged from 90 to 600 mg. per day, given in divided doses, preferably every three hours, but at most every two hours. The average dose was found to be from 200 to 400 mg. per day, which represents one 50 mgm. tablet five times a day. Toxic effects were frequent and occurred in two-thirds of the patients, and it was necessary in one-fifth of the group to stop treatment on this account. The toxic symptoms encountered in order of frequency were, "giddiness," nausea and epigastric "burning," feeling of lightness of the legs and a sensation of floating. Dunham and Edwards[9] confirmed the lessening of rigidity in patients on parpanit and considered that its ac-

tivity was comparable to that of the solanaceous alkaloids, but some patients found its side-effects, of which the most prominent is a sensation of dizziness, less upsetting.

Sciarra, Carter and Merritt[28] after using parpanit in twenty-eight patients with Parkinsonism reported that none of them showed objective improvement, and in only one patient was there subjective improvement. Toxic side-effects were encountered in 86 per cent of the patients on whom the drug was used.

Comment.—This drug has proved to be of limited value in our hands in the treatment of parkinsonism. It is not routinely employed. The high incidence of toxicity is a relative contraindication to its widespread usage.

4. *Artane* (trihexphenidyl, or 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride).—In general, the reactions of artane resemble those of atropine. However, it is entirely free of the toxic effects of atropine on the cardiac vagus, blood pressure and circulation.[6] Doshay and Constable[6] after investigating its use in 117 patients with parkinsonism concluded that artane was "the drug of choice in the arteriosclerotic and idiopathic cases, and should be tried regularly in postencephalitic cases in which atropine or other forms of medication prove disturbing or ineffectual." The usual dose used was between 6 to 10 mgm. per day—with doses as high as 50 mgm. per day being used without deleterious effects. The toxic symptoms encountered included dryness of mouth, blurred vision, nausea or vomiting, dizziness or giddiness and drowsiness. Corbin[3] reported on its use and found that of sixty-nine cases with idiopathic paralysis agitans fifty-three were benefited, and of seventeen post-encephalitics twelve obtained some relief. The drug appeared to act by relaxing rigid muscles and in some cases tremor also was improved. The side-effects, usually slight, were, in order of frequency, dry mouth, nausea, "giddiness," blurring of vision, nervousness or "jitteriness," tinnitus, "tightness in the head" and soreness of the mouth. Four patients had severe and immediate toxic reactions; namely, mental confusion, dizziness with nausea, and marked agitation. The average daily dose used by Corbin was 8 mgm.

Schwab and Tillmann[31] treated forty-four patients with artane for three months and found it improved the condition of twenty-nine, but in most of them it had its greatest effect when given in conjunction with parpanit, benadryl, or an atropine preparation.

Comment.—This drug has proved to be a valuable addition to the therapy of parkinsonism. At the commencement of treatment three of the 2 mg. tablets are prescribed daily. This is increased by 1 tablet every other day until the patient is taking 6 mg. three times a day. The pills are best tolerated when taken after meals. We have not found it ordinarily beneficial to exceed this dosage. However, in the occasional case, additional benefit is obtained from increasing the dosage. This drug is particularly welcomed by the older age groups because of the low incidence of toxic side effects. In this regard, the most troublesome and potentially dangerous side-effect is that of a toxic encephalopathy. We have encountered six such cases to date, one of which terminated fatally. It is frequently necessary after a period of artane therapy to add one of the drugs of the belladonna series as the effect of artane appears to wear off when administered alone.

5. *Tolserol (myanesin):* (3-orthotoloxy-1,2-propanediol).—Favorable results following the use of this drug in the treatment of parkinsonism have been reported.[1,20,21,29,37] Toxic symptoms were rarely encountered and consist of (1) complaints of weakness, either in the arms or legs accompanied by a feeling of lassitude,[29] (2) nausea in one case,[21] (3) leukopenia in two of eight cases.[13] Early British investigators reported the presence of hematuria and hemoglobinuria but this has not been found by investigators in the United States. Tolserol is available in oral preparations, as suppositories, and in a 2 per cent solution for intravenous administration. Jeub[21] reports the effect of an oral dose as transitory, wearing off in forty minutes.

Comment.—This drug has proved to be of no use in the treatment of parkinsonism in the patients followed in our clinic.

6. *Antihistaminic Agents.*—Budnitz[2] reported a beneficial effect from benadryl in the treatment of eight cases of paralysis agitans of the arteriosclerotic group. Ryan et al,[27] reported similar beneficial effects from the use of benadryl in the treatment of forty cases of parkinsonism.

Comment.—Our experience with benadryl and the other antihistamines indicates that they are

of limited use in the treatment of parkinsonism. However, in some cases, some additional benefit is derived by the addition of 50 mgs. of benadryl three or four times a day to the medication which the patient is receiving. The sedative effect of the drug is gratifying when the patient is tense. It should be emphasized that if benadryl is used, it should be used in conjunction with other medications.

7. *Diparcol* (diethylamino, 2, ethyl-N, dibenzo-para-thiazine hydrochloride).—The use of diparcol in the symptomatic treatment of Parkinson's disease was described by Sigwald, Bovet and Dumont[35] in November, 1946, at a meeting of the French Society of Neurology. In a later paper[36] the same group of investigators reported on 168 patients who had been studied carefully. They claimed satisfactory and frequently dramatic results in 53 per cent, good results in 24 per cent, and fair in 17 per cent. Only 6 per cent of their patients represented therapeutic failures. They felt that the clinical response was substantially more gratifying than had been obtained previously with earlier drugs. Some improvement in symptoms has also been reported by other observers[5,32] but the side-effects of this drug will probably prevent its widespread usage: they include severe vertigo, paresthesia in the legs, somnolence, transient paralysis lasting about an hour,[10] nausea, vomiting, hyperthermia, and leukopenia.

Comment.—Because of the high incidence of toxicity, this drug has been used only to a limited extent in the parkinsonism clinic. However, some patients who have failed to respond to all other medications derive excellent symptomatic relief from the diparcol. Its use should be restricted to the patients in whom all other medications have proved of no avail.

8. *Benzedrine.*—In 1935 Prinzmetal and Bloomberg[26] used benzedrine in treatment of narcolepsy. Since then it and more recently dexedrine have been used in the treatment of oculogyric crises, psychic abnormalities and lethargy.[41]

Comment.—Both benzedrine and dexedrine are useful in the management of oculogyric crises, mild depressions and somnolence and lethargy. The usual dosage is 5 mgs. of either of the drugs, two or three times a day. If the medicine is well tolerated, it may be increased to 10 mgm. two or three times a day. It is important not to prescribe benzedrine or dexedrine after 4 p.m. as administration after this time frequently prohibits the patients from sleeping. Benzedrine and dexedrine are usually given in combination with other drugs directed towards relief of the tremor and rigidity of parkinsonism.

9. *Lysivane* (Parsidol): (diethylamino-propyl)-n-dibenzo-parathiazine hydrochloride).—In September of 1949, Sigwald[34] reported upon the use of lysivane in the treatment of 106 patients with parkinson's syndrome. He stated that the drug gave a greater percentage of symptomatic improvement than any other treatment used in these patients. In six patients, he found it necessary to terminate the therapy because of severe toxic symptoms such as painful cramps, palpitations and very severe dizzy spells. Gallagher and Palmer[12] subsequently reported favorably upon the use of lysivane in forty patients and felt that on the whole it was superior to artane. They noted minor effects of drowsiness and transient giddiness from the drug but in no instance was it necessary to terminate treatment because of the toxicity.

Comment.—Our experience with this drug has been limited to ten cases. In two cases, there has been a result superior to that obtained with the other medications which the patients had received. A further period of observation will be necessary to determine the therapeutic effect and toxicity of this drug.

Summary

In commencing drug therapy in parkinsonism, one of the following drugs is recommended: Vinobel, rabellon, bellabulgara, hyoscine or artane. It may be necessary to try each of these drugs in turn before satisfactory control of the patient's symptoms is obtained. Additional symptomatic relief can on occasion be obtained by the addition of benzedrine, dexedrine, benadryl or atropine to the above medications. In the occasional patient who fails to respond to various combinations of the above medications, the use of parpanit is worth a trial. The experimental drugs, diparcol, dihydro-beta-erythroidine and lysivane, are not yet available for general usage.

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Most people resist education and only the few seek it. Educators tell us there are three periods in life when the individual is very ready to learn: (1) the little child who is eager to learn everything; (2) the young mother who wants to learn how to care for her child; (3) the person who is ill and is very anxious to learn how to regain his health. The patient is a member of a community; he is anxious to learn how to get well and stay well, but he cannot learn without a teacher. The logical persons to reinforce the formal instruction which the patient receives, whether that instruction be given by the doctor or a nurse, are the members of the nursing staff in their daily contacts with the patient.—AILEEN FLETT, R.N., Canadian Tuberculosis Association, May, 1951.

SIMPLE PROCTOLOGIC PROCEDURES

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THE diagnosis and treatment of many disorders of the anorectal region fall within the scope of activity of the general practitioner and the general surgeon. This paper will have accomplished its purpose if some of its readers will have been stimulated to explore the possibilities suggested herein.

An accurate diagnosis is essential to the proper care of any disease condition. Especially is this true in the realm of anorectal diseases. Proctoscopic examinations have been available for many years. The procedure is a relatively simple one, and yet few people are given the benefit of this examination—even today. The time has come, however, when the proctosigmoidoscopic examination must be included as an integral part of every complete physical examination. Only in this way can we hope to improve the care which we give to our patients and to recognize and treat neoplastic diseases before the patient is confronted with a hopeless prognosis.

The present era should be referred to as the "proctoscopic era" because the importance of this examination is presently being recognized, and the procedure is rapidly assuming its rightful place in general physical surveys. Although the digital rectal examination is still a very important part of every physical examination, it cannot be considered an adequate means of investigating the lower bowel. Experience has taught that the proctosigmoidoscopic examination is the only accurate method at our disposal to evaluate the status of the rectum, rectosigmoid and lower sigmoid areas.

The time has come also when we should reevaluate the status of the barium enema x-ray in the diagnosis of lesions of the rectum and lower colon. Radiologists have warned time and again that the x-ray should not be depended upon to pick up or to rule out lesions in the rectal or rectosigmoid areas. Radiologists in increasing numbers are stressing the necessity for sigmoidoscopic examinations when there is a question of a lesion in that area. Yet, for some reason which is difficult to explain, physicians still send patients for x-ray studies of the colon as an initial procedure when symptoms point to trouble in the rectal or rectosigmoid areas and when a proctoscopic examination could easily and quickly supply the necessary information. The barium enema x-ray examination furnishes us with the only satisfactory means of visualizing the interior of the large bowel above the lower sigmoid colon and should be used routinely to supplement the information obtained from the proctosigmoidoscopic examination. It is extremely important to keep the fact in mind that 70 to 80 per cent of all large bowel disease is present in the lower sigmoid and rectal areas and that it is precisely in these areas that the x-ray is of questionable value. It would be well for all physicians to recognize that the indications for x-ray studies of the colon are *ipso facto* indications for proctosigmoidoscopic examinations.

Physicians interested in performing the proctoscopic examinations find little difficulty in learning the technique. The younger men are taught to perform the examination in the junior and senior years of medical school, and there is ample opportunity to practice the procedure during the internship. The physicians already in practice can, with a reasonable amount of effort, become proficient in the technique after a short period of time. The examination need not be a very painful experience for the patient. The physician should attempt to prepare the patient psychologically before the examination. If this is done, and if the examiner will carry on a running conversation during the examination to permit the patient to understand just what is occurring, the patient will relax and co-operate satisfactorily.

There are a few dangers that should be pointed out, and there are a few general rules that can be followed to avoid these dangers. In the performance of a proctosigmoidoscopic examination, one must be mindful of the fact that he is introducing a rigid metal tube into a hollow viscus and that perforation of the viscus may result. The peritoneal reflection on the anterior rectal wall sometimes reaches to very low levels and one cannot tell in a given case just where the reflection is located. Should perforation of the

Read at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

anterior rectal wall occur it is best to open the abdomen to make certain that the peritoneal cavity has not been entered. Perforations of the sigmoid colon always involve the peritoneal cavity and in the event of a sigmoid perforation the abdomen should be opened promptly and the perforation closed. If this is done within a few hours of the perforation, a proximal colostomy may not be necessary. If, however, a greater period of time has elapsed and there is evidence of peritonitis, a proximal colostomy should be performed at the time that the perforation is closed.

The following rules of safety should be observed when conducting proctosigmoidoscopic examinations:

1. A digital examination should precede every instrumental examination of the rectum. If the digital examination is done with a well-lubricated finger and gently performed without producing pain, the patient will be psychologically prepared for what is to follow. On the other hand if the digital examination is a painful experience for the patient, the subsequent instrumental examination will have to be performed under circumstances which are far from desirable. The patient will be tense and afraid, his muscles will be contracted, and the examination will be difficult to perform.

2. The obturator of the scope should be withdrawn as soon as the scope has passed beyond the grasp of the sphincters. From here on, the scope should be advanced only under direct vision.

3. Air insufflation should be used with caution. The use of air is a helpful adjunct in finding the lumen of the bowel but overdistention with air may cause disruption of the bowel wall or frank perforation. This is especially true in those patients in whom the bowel is already weakened by inflammatory processes or tumors. In patients suffering from ulcerative colitis or carcinoma the use of air insufflation is particularly hazardous.

Many of the procedures used to correct or alleviate anorectal disorders are quite simple insofar as techniques are concerned. When a complete examination of the entire rectum and lower colon has been performed, the following conditions will have been found in a large percentage of cases:

1. Rectal adenomas or polyps.
2. Hemorrhoids: internal, external and combined types.
3. External thrombotic hemorrhoids.
4. Anal fissure.
5. Perianal abscess.
6. Perianal fistula.

Rectal Adenomas or Polyps.—Polyps of the rectum and lower colon have been found in approximately 10 per cent of all healthy adults examined in the cancer detection centers throughout the country. Polyps are frequently found also in children and young adults who are examined on account of bleeding from the rectum. Since it is believed that all polyps in this area are premalignant, it is essential that they be diagnosed as early as possible and that proper treatment be instituted. Nonmalignant polyps in the rectum can usually be removed through the proctoscope as an office procedure. Since the rectal mucosa is devoid of sensory nerve endings, these polyps can be fulgurated without pain. Pedunculated polyps should be removed with some type of snare so that the polyps can be sent to the pathologist for microscopic section. Biopsy of the nonpedunculated polyps is also desirable to rule out the possibility of malignant changes. The destruction of polyps above the rectosigmoid area is best performed in the hospital since the danger of perforation is always present.

Hemorrhoids. — Most hemorrhoids are best treated by some type of surgical excision. There are several excellent techniques available which produce good results with short periods of disability and very little discomfort. Except for the excision of thrombotic external hemorrhoids and the injection treatment of internal hemorrhoids, patients should be sent to the hospital for this type of surgery. It is better for the physician to learn one method well than to try to adapt parts of various methods for a given case. A hemorrhoidectomy well performed and properly cared for during the healing period produces a very grateful patient. Poor results from hemorrhoid operations can usually be ascribed to lack of postoperative supervision of the wounds rather than to an inadequate surgical procedure. However, it must be borne in mind that a basic knowledge of the anatomy and physiology of the anorectal region is of paramount importance if one

is to avoid the pitfalls of irreparable damage to the sphincter mechanism of the anal canal. The excision of hemorrhoids is usually a very simple procedure. The repair of a damaged sphincter, however, is usually a major surgical accomplishment.

The injection treatment of hemorrhoids remains a satisfactory and ethical method of treating a certain type of hemorrhoid. If the treatment is limited to the internal type of hemorrhoid which is not complicated by infection, stenosis or other type of lesion a good result can be anticipated. The poor results which are commonly seen are the result of the use of the injection treatment for hemorrhoids which do not fall into the above category. Quinine and urea hydrochloride (5 per cent and 5 per cent phenol in olive oil are the solutions most commonly used for the injection treatment. Sloughs and hemorrhage are the two complications most frequently seen, and these can be avoided by placing the solution in the proper place and by avoiding the injection of too large a volume of the solution.

Thrombotic External Hemorrhoids.—Thrombotic external hemorrhoids can usually be treated in the office. The clot of blood which produces the distention and pain only occasionally lies free beneath the skin and can be extruded through a linear incision. Most of the clots are firmly attached to the deeper tissues and are diffusely spread through the hemorrhoidal tissue in the distended mass. For this reason it is best to infiltrate the area around the hemorrhoid with a local anesthetic agent and to uncap the hemorrhoid rather than to incise it. The entire mass of hemorrhoidal tissue containing the clot can then be removed and a permanent result will be obtained. Sutures are required only if troublesome bleeding occurs.

Anal Fissure.—True anal fissures usually result from a combination of intrinsic pathological processes in the anal canal. The cure of the anal fissure is dependent upon the correction of the anal pathologic condition which produced the fissure. The application of ointments and the use of suppositories or silver nitrate solutions cannot be considered adequate treatment for anal fissure. Most fissures are secondary to infected anal crypts which have become traumatized by hard, constipated stools or explosive liquid movements. The surgical excision of the fissure should include the infected crypt and the resultant scarred area if present. Faulty bowel habits should also be corrected in order to assure a permanent cure. The surgical treatment of anal fissure is usually a simple procedure but must of necessity be radical enough to accomplish a proper end result. Inadequate treatment of this condition leads to unnecessarily long periods of disability. The injection of a long-lasting anesthetic solution beneath an anal fissure may give temporary relief from symptoms but does not usually lead to a cure of the fissure itself.

Perianal Abscess.—Abscesses appearing in or near the anal canal usually originate in the region of the pectinate line and travel subcutaneously to rupture or be drained externally. These abscesses should be drained or uncapped as soon as the diagnosis is made to avoid further destruction of the sphincter muscle fibres and the supporting tissues. A wound which is large enough to remain open without packing is preferable to simple incision since it serves to terminate the spread of the infection more adequately. Linear incisions tend to close over rapidly, and when this occurs, the infection continues to spread. A large percentage of these abscesses terminate as perianal fistulas. It is always a good policy to advise the patient of this fact so that he will anticipate a second operation for fistula. Patients do not take to the second operation kindly if they have been made to feel that the first operation did not accomplish the desired result. Except for the small abscess which is very fluctuant, the majority of these cases are best treated in the hospital where adequate anesthesia is available.

Perianal Fistula.—The fistulous tract resulting from a perianal abscess which was properly handled is usually a simple one. In other words, if the abscess was opened early in the course of the disease and before it had an opportunity to spread in different directions, the tract in all probability would be quite direct in its course. The cure of fistula-in-ano is always surgical. The tract must be laid open in its entirety although it is not essential to excise the floor of the fistulous tract itself. Wounds should be created that will remain open without packing, and these wounds should be kept as clean as possible during the

(Continued on Page 1046)

Rh INCOMPATIBILITY ACCOMPANIED BY ACUTE RENAL FAILURE

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THE NECESSITY of more detailed Rh blood typing in prevention of acute renal failure was recently impressed on the staff of the University Hospitals by the appearance of a near fatal reaction in an Rh negative patient who received 1,000 cc. of Rh positive blood during an operation. These are preventable catastrophies which, in the light of present knowledge, should no longer occur in modern hospitals. It is the purpose of this report to document one such occurrence caused by failure to detect blocking antibodies in recipient serum, to describe means of preventing future accidents, and to outline briefly the management of this case.

Levine and Stetson,[4] on the basis of clinical experience in 1939, postulated the occasional presence of a hitherto unrecognized agglutinogen responsible for the sensitization of the mothers of erythroblastic infants. Subsequently, Landsteiner and Weiner,[3] in 1940, identified the Rh factor and Weiner and Peters,[11] observing this factor to be antigenic in Rh negative individuals, related it to the unnamed factor of Levine and Stetson.

Further researches[2,6,10] independently demonstrated that antibodies against the Rh factor usually agglutinate Rh positive red blood cells if the latter are suspended in specific protein media. These antibodies are referred to as albumen agglutinins, heat stable antibodies, or blocking antibodies. When antibodies cause agglutination of a saline suspension of erythrocytes they are designated saline or heat labile antibodies. To detect antibodies, the test red blood corpuscles can be suspended in serum, plasma, bovine albumen, or the Coombs[1] test may be applied. The following case report demonstrates the interference of blocking antibodies in a cross-matching procedure improperly designed to detect their presence.

Case Report

L. E. (U.H. 821510), a forty-seven-year-old white housewife was operated upon at the University Hospitals for a tumor at the angle of her right jaw which proved to be a malignant lymphoblastoma in the parotid gland. 1,000 cc. of blood was given during the procedure. On the third postoperative day icterus and anuria were noted, and the diagnosis of acute renal failure was established. Up to this time, the patient received 3,000 to 4,000 cc. of glucose 5 per cent in distilled water daily. From this point on fluid intake given as I.V. 50 per cent glucose solution was restricted to replacement of insensible fluid losses (Table I). In this fashion, a caloric intake of about 2,000 calories was provided daily despite persistent nausea and vomiting. The urine output rose to 50 cc. on the day following complete anuria and increased progressively to 1.5 liters on the fifteenth postoperative day.

Diuresis followed with formation of 6 liters of urine on the nineteenth postoperative day. Overhydration as assessed by mild pitting edema and increased body weight during the anuric phase was present from the second postoperative day and was not fully corrected until the twenty-first day after operation. Delay in establishing the diagnosis of lower nephron nephrosis, and parenteral fluid replacement with three to four liters of 5 per cent glucose in distilled water daily was responsible for the inadvertent overhydration in this patient. It is interesting to note the greatest depression of sodium and chloride occurred on or about the ninth postoperative day when the overhydration state was maximal as assessed by weight. This suggests that hemodilution plays a rôle in lowering the concentration of serum values of sodium and chloride. When diuresis was established these values rose toward normal, even though salt intake was restricted to less than the urinary losses of sodium chloride.

Discussion.—Retrospective investigation revealed the patient to be actually Rh negative and sensitized by two previous pregnancies. Her blood contained a high titer of antibodies that proved to be of the blocking variety. The patient was mistyped Rh positive and crossmatching methods used at that time did not provide a specific check for this kind of mistake. The procedure for typing and crossmatching at our hospital prior to the hemolytic reaction of this case was as follows:

1. Slide typing using anti-A, anti-B, and anti-D (anti-Rh) sera.
2. Cross-match in test tubes with incubation at 37°C for one hour. In one of two tubes was placed a mixture of donor's cells and recipients' serum in saline; in the other a

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TABLE I.

Surgery—1000 cc. Whole Blood I.V.

Postoperative days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	23	25	26
Daily urine volume	500	500	0	50	50	50	100	100	120	245	350	475	775	1500	1400	2250	2600	4000	6000	5840	5250	3975	5100	5900		
Gms. NaCl in urine														5.5	7.4		10.2		21.6	16.8		16				
Body weight			124	126	128	131	130	130	131	132	131	130	130	129	129	128	127	125	121	120	120	117	115	116	116	117
Parenteral fluids—liters	3.0	4.0	3.1	2.7	0.9	1.0	1.4	1.0	1.0	0.6	1.0	1.0	1.2	1.2	1.5	1.0	2.9	3.5	4.4	4.3	5.0	7.9	4.6	3.7	6.6	
NaCl administered			4.5	4.5				4.5	4.5	4.5	4.5	4.5	9	4.5	0	4.5	4.5	9	9	18	4.5	18	18	9	18	
50% Glucose administered							1000	900	500	500	1000	1000	1250	1000	750	750										
BUN				80	92	100	125	135	128	122	134	120	139	144	168	140	173	153	125	138	93	87	73	67		
CO_2				21	23	19	21	21	17	18	17	17	17	14	16		17	18	16	19	18	19	19	22	23	
Cl				79	72	71	66	65	67	72	72	75	82	77	83		92	88	87	83	99	96	100	107	111	
Na								112	102			124	124		120	118	126	131	130		130	131	133	144	142	
K				4.7				4.3	4.6			5.1	4.5		4.9	4.8	4.8	4.6	4.7		4.0	3.3	3.3	3.1	3.2	

mixture of donor's serum and recipients' cells in saline.

3. If the blood was found to be Rh negative on typing, an additional test was done. A mixture of saline, anti-D serum and the donor's or recipient's blood were incubated for one hour at 37°C.

Recent changes of procedures in our blood bank include a test tube Rh determination on all bloods (step 3, above) since cold agglutination and rouleaux formation on slide typing are readily mistaken for true agglutinations. The saline suspension used for this test greatly reduces the probability of pseudo-agglutination and will correct the mistyped bloods from the slide test. In addition the standard cross-match (step 2 above) has been replaced by the serum cell method of cross-matching in which serum is used for the cell suspension in place of saline to identify blocking antibodies. Our patient's blood contained blocking antibodies which could have been detected accurately by this method. This test will also detect the small group of Rh positive individuals who have been sensitized by Hr antigen.

Experience with this and subsequent cases has made us increasingly aware of the importance of prevention of overhydration during anuria. Earlier authors attempted to resolve anuria by forcing fluids. Their report too often was: "in spite of injection of massive quantities of glucose and saline, the patient died of uremia and pulmonary edema." In the absence of fluid losses only 500 to 800 cc. of water needs to be replaced daily to maintain a 70 Kg. anuric patient in fluid balance.

The accumulation of metabolic products is not the important feature of this syndrome toward which therapy should be directed as Strauss,[8] Stork,[7] Thorn[9] and Muirhead[5] have emphasized. Available evidence indicates that death does not occur from retention of urea per se. Stork[7] found no correlation between death and height of blood-urea-nitrogen or non-protein nitrogen. Strauss[8] cites many cases of complete anuria from mistaken removal of a single kidney, carcinomatous obstruction of both ureters, and other causes in which the patients lived from five to seven weeks. It is of interest to note that these cases were reported in the older literature prior to the use of parenteral fluids. Death with lower nephron nephrosis since the era of parenteral fluid therapy, has usually occurred within eight days, and these patients invariably demonstrate pulmonary and generalized edema and increased body weight.

The development of hyperkalemia during anuria should be anticipated. If fluid and food are given orally, care must be taken to avoid the administration of potassium as contained in bouillon or fruit juice. Intravenous glucose and insulin may be helpful in treating hyperkalemia, but its effect is short lived. The artificial kidney appears to be an effective means of controlling hyperkalemia which appears during anuria. Increasing success with conservative management, however, both here and in other clinics, sharpens our awareness of the dangers inherent in the anuric patient. Strict control of hydration is probably the most important factor responsible for these successes.

Summary

The presence of blocking antibodies was recently responsible for failure to detect a mistake in Rh typing in our hospital. A hemolytic transfusion reaction resulted when the patient received

1,000 cc. of Rh incompatible blood during surgery. Complete anuria developed on the third postoperative day and a return to adequate urine output was delayed until the fourteenth day after operation. A moderate overhydration developed in our patient due to the two-day delay in detecting renal damage, and the necessity of giving fluids only in sufficient amount to replace insensible losses is stressed.

Modifications in the blood bank procedure include: (1) Performance of a test tube Rh determination on both Rh negative and Rh positive bloods, whereas formerly only Rh negative bloods were tested further in this manner. The mistyping of our patient could have been detected by this test. (2) Replacement of the saline suspension cross-match with the serum suspension method effectively detects blocking antibodies.

An incompatible blood transfusion has not been administered in this hospital in the two years since the above scheme has been utilized.

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TREATMENT OF THE CONVULSIVE DISORDERS

(Continued from Page 1030)

Conclusion

The treatment of the "epileptic" patient requires an adequate medical examination, use of diagnostic procedures to determine the most likely etiology, and administration of the specific drugs in adequate dosage. These measures should be followed with rehabilitation of the individual in every respect in order that the convulsive patient may become a social and economic asset. Treatment of the convulsive disorder requires treatment of the total personality.

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TREATMENT OF CONDUCTION DEAFNESS WITH ROENTGEN THERAPY

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THE PURPOSE of this paper is to discuss the treatment of conduction deafness with roentgen therapy and to review our experience at the Mankato Clinic with this form of therapy. We have used roentgen therapy in the treatment of chronic eczematoid external otitis and nasopharyngeal malignancy as a cause of impaired hearing, but in this paper we are concerned primarily with the use of x-ray in the treatment of nasopharyngeal lymphoid hyperplasia as a cause of conduction deafness. The literature concerning the use of radium in this condition is voluminous. However, little has been said and written about the use of roentgen therapy. Doctors Crowe and Burnam of Johns Hopkins University popularized the modern use of radium and its use has been only comparatively recent. A few national authorities in otology have stated that they are afraid of the use of radium, and that its use is only a passing fancy. Roentgen therapy has been used for many decades, and it is still used. Apparently its use is not a passing fancy.

The first report of x-ray therapy to the throat and auditory tube area for deafness that I can find is that by Jarvis[4] in 1923. He mentions the case of an adult patient who volunteered the information that the right ear which had been "stuffy" for ten years was clear, and that hearing was improved one week after x-ray treatment of the lingual tonsil. Jarvis found that prominent lymphoid nodules on the posterior pharyngeal wall and prominent lateral pharyngeal bands had decreased in size and redness forty-eight hours after exposure to roentgen rays. However, roentgen rays had been applied directly to the middle ear for treatment of tinnitus and chronic otitis media as early as 1904 by Joseph Beck of Chicago.[7] Jarvis further found that the type of patient subject to frequent head colds with more or less constant postnasal drip and frequent intervals of stuffiness in the ears with an accompanying impairment of hearing responded best to the use of roentgen rays. In the light of more modern knowledge, Jarvis' theory that the beneficial effect of x-rays in these cases was due to its effect on the bacterial content of the throat is not plausible. We have found x-ray useful in the same type of patient described by Jarvis. However, many of these patients are allergic and have evidence of functional autonomic imbalance. I submit that x-ray is helpful in these cases not only because it decreases the size of obstructive lymphoid tissue, but also reduces the function of the end organs of the autonomic nervous system. In other words, x-ray reduces the function of mucous and serous glands so that autonomic imbalance or allergy cannot stimulate these glands to hyperfunction. This is a similar action to that of chemical or electrical cautery of boggy wet inferior turbinates in vasomotor rhinitis. The number and effectiveness of secretory glands in the turbinates is reduced by cautery.

Degenerative changes in lymphocytes have been demonstrated a short time after exposure to x-ray radiation which produces degenerative and destructive tissue changes by ionization in the cells. Microscopic examination of adenoids which had been irradiated before removal shows that the action of the radiation is confined to the cells of the germinal centers. A few days after irradiation the cells show chromatolysis and fragmentation of the nuclei. Since the life span of the mature lymphocytes is very short—as low as twelve hours according to some authorities—the mass of the adenoid tissue gradually shrinks since there is no replacement from the damaged germinal centers by new lymphocytes. Schenck[10] has stated, and I quote, "More attention must be directed to the concomitant changes in the lymph channels and lymph vessels. Obstruction of lymph channels and lymph vessels occurs in the course of chronic infection by invasion of fibroblasts, constriction of fibrous tissue, and proliferation of endothelium within the lymph channels. Such obstruction to normal lymph flow must have significant effects upon contiguous lymph structures and the areas normally served by them. Irradiation produces striking effects upon the endothelium of the lymph vessels. Destruction of some endothelial cells

Read at the Annual Meeting of The Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

occurs and the remaining cells appear contracted. The effect on occluded lymph vessels with multicellular walls is the conversion to channels with incomplete unicellular walls which permit the passage of lymph." Such action by x-ray radiation would eliminate obstructive passive lymph congestion in the auditory tube from lymphoid hyperplasia within the tube as well as in and about the auditory tube orifice. X-ray radiation has a cumulative effect. Its maximum effect is not fully apparent until about two weeks after the last treatment. For this reason we try to see the patient at the end of the x-ray treatments, and one, three, and twelve months after treatment. I have no pictures to show reduction in the size of lymphoid tissue after x-ray radiation, but by careful examination of the nasopharynx with the postnasal mirror and nasopharyngoscope using 2 per cent Pontocaine topically when necessary; we have seen gross changes occur after the radiation. Lymphoid tissue does decrease in size and auditory tube orifices blocked by a red, edematous mucosa and irregular hypertrophy of the torus tubarius have been seen to return to a normal appearance, wherein the torus is smooth and round, and the orifice itself presenting patency and a smooth pale mucosa in its floor and immediate edges. I have seen this normal appearance of auditory tube orifices in routine examination of the nasopharynges of patients who have no difficulties in their ears or throats.

The use of radium in the treatment of lymphoid hyperplasia of the nasopharynx as presented in extensive papers by Crowe, Burnam, Fowler, Boies, is not within the scope of this paper. An excellent symposium on Irradiation of Lymphoid Tissue of the Nasopharynx was given at the American Academy of Ophthalmology and Otolaryngology in October, 1949. It was shown that radium is of help in managing conduction deafness due to auditory obstruction from lymphoid hyperplasia. The dangers of handling radium was emphasized. Day pointed out in that symposium that the radium applicator was being used indiscriminately, and that this would result in more harm than good.

Roentgen therapy does have certain advantages over the use of radium in the management of deafness. Lampe[5] stated that the 50 mg. radium monel metal applicator inserted in the nasopharynx for twelve minutes delivers a dose of 4,428r at the surface. This dose is higher than the dose the experienced radiation therapist will use in the treatment of benign conditions. It is a cancerocidal dose used for lymphoid hyperplasia, which is a benign lesion. Lampe has stressed the possible danger of this dose not only to the patient but to the otologist who handles the radium. In roentgen therapy the dose delivered both at the skin and in the nasopharynx is below that of a cancerocidal dose. Our cases are treated by a certified roentgenologist who is well protected from the irradiation. Decker[1] urges that radium be used with great care and only by those qualified to use it. He believes that its scope of action is so small and so limited that if the lymphoid tissue extends beyond the small distance reached by the radium, success will not be achieved. For this reason he leans toward roentgen irradiation as being more inclusive and generally more effective than radium. Lymphoid tissue does extend along the auditory tube beyond the small distance reached by radium. Fowler[3] found microscopic evidence of lymphoid tissue in the peripheral portion of the auditory tubes and the middle ears of aviators killed during World War II. These microscopic slides were exhibited by the Army Institute of Pathology at the American Academy of Ophthalmology and Otolaryngology in 1949, and in many of these slides considerable collection of lymphoid masses were seen along the auditory tubes. Lindsay has stated before the Minnesota Academy of Ophthalmology and Otolaryngology that this tissue is not significant yet there is no reason why it cannot hypertrophy as well as the lymphoid tissue in and about the auditory tube orifice. In the work of Haines and Harris with submarine trainees during the last war it was found that 25 per cent of submariners who had open tubal orifices as seen by the nasopharyngoscope suffered grade-four damage to the middle ears in pressure tests. This would lend evidence to the fact that obstruction can be located in the peripheral portion of the auditory tube beyond the scope of action of radium. Roentgen therapy, however, will reach this obstruction. Farrior[2] has described various tests to determine the degree of auditory obstruction. These show peripheral auditory obstruction in many cases with no visible evidence of obstruction at the auditory tube orifice. Farrior states that roentgen radiation is indicated in these cases. Our own series of cases include three patients with conduction deafness from auditory obstruction and yet with no evi-

dence of obstruction at the auditory tube orifice as seen by the postnasal mirror and the nasopharyngoscope. Their hearing was definitely improved by the use of roentgen therapy. Besides the very limited scope of action by radium, namely not over one cm., I am sure, we are all familiar with the great difficulty in placing the radium applicator immediately at the auditory tube orifice. In addition to lymphoid tissue existing in the periphery of the auditory tube, Robison has proposed that a nasopharyngeal lymph node in the region which the auditory tube traverses, can cause pressure on and displacement of the lumen of the auditory tube. Only roentgen therapy, of course, would reach such a lymph node. Other advantages of roentgen therapy over the use of radium are the relative ease of roentgen therapy and the freedom from fright that is connected with the insertion of the radium applicator.

Certain disadvantages or objections to the use of roentgen therapy have been raised in the past. One of these is that roentgen therapy will cause pituitary dysfunction. However, by examining a skull and considering the technique used, it can be easily seen that the pituitary gland is well above the path of the x-rays. Another objection is that x-ray must penetrate normal tissue to reach the nasopharynx and auditory tube. However, the normal tissue penetrated can withstand a much higher dose of x-ray than that used to shrink lymphoid tissue. A third objection is that x-ray will harm ossification centers. The only ossification center that receives any exposure to the x-ray is that in the condyle of the mandible. This center is united at the fourth month of fetal life.

Possible undesirable effects of roentgen therapy are dryness of the throat, swelling of the parotid gland, and nausea and vomiting. These effects have been seen occasionally but they have been transitory in duration. No permanent harmful effects have been seen from roentgen therapy.

Roentgen therapy in our cases is given by a certified roentgenologist. In the technique of treatment he places a rubberized lead shield with a 6 x 8 cm. portal over one side of the patient's head. The center of this portal is located at the angle of the mandible. The roentgen rays are directed inwards and slightly upwards through this portal to reach the entire auditory tube as well as the nasopharynx. Two hundred kilovolts are used. The target skin distance is 50 cm. and the rays are filtered by .5 millimeters of copper and 1 millimeter of aluminum. In adults a total dosage of 600r measured in air at the skin is given on each side of the head in four divided doses given over a two-week period. In children the total dose is 400r on each side. This gives a total dose of 318 to 366r at the nasopharynx in adults and 212 to 288r at the nasopharynx in children. Considering the cross-firing principle this dose is adequate to reduce lymphoid tissue in size. It is also a safe dose.

Results of the use of roentgen therapy in the management of conduction deafness have been good. In 1948 Youngs[11] reported 116 cases of conduction deafness treated with roentgen therapy. These patients varied in age from three to sixty-two years. Forty-six or 39.6 per cent of these regained normal hearing after roentgen therapy as determined by periodic audiograms, whispered voice, and tuning fork tests. Twenty-five or 21.5 per cent received marked improvement in hearing. Twenty-three or 19.8 per cent received some improvement and twenty-two or 18.9 per cent received no improvement of hearing. Richardson's[8] records based on 600 cases showed improvement from a slight degree to a complete recovery of normal hearing in not less than 60 per cent of a mixed group of cases. In 1937, O'Brien[6] reported seventy-three cases of chronic catarrhal deafness of a group of 140 with varying degrees of deafness as improved by roentgen therapy. In 1949, Rosenberger[9] reported twenty patients with impaired hearing treated with roentgen irradiation. One-third of these had significant benefit from such treatment after standard otologic treatment had proved ineffective.

Since March, 1949, 109 patients have received roentgen therapy to the nasopharynx at the Mankato Clinic. Several of these patients have been referred for treatment by doctors outside the Clinic, and their records are not available. Some of these patients have been given roentgen therapy for reasons other than auditory tube obstruction with conduction deafness. Fifty-four of these patients were given roentgen therapy because of conduction deafness secondary to auditory tube obstruction and with or without evidence of lymphoid hyperplasia. Thirty-two of these fifty-four patients returned for follow-up study. These thirty-two patients had had conduction deafness from about three months to about ten years and varied in age from five to fifty-three years. Most of them had lymphoid

hyperplasia in and about the auditory tube orifice and all of them had signs of auditory tube obstruction. They had repeated audiograms, tuning fork tests, whispered voice tests, and nasopharyngeal examinations by the postnasal mirror and nasopharyngoscope before and up to one year after roentgen therapy. Study of their records shows that of these thirty-two patients eighteen or 56.25 per cent regained normal hearing after roentgen therapy, six or 18.75 received marked improvement in hearing, three or 9.37 per cent received slight improvement in hearing, and five or 15.62 per cent experienced no change in hearing after roentgen therapy. In all of these patients, examined repeatedly one month to one year after roentgen therapy, there was either complete recovery of the normal appearance of the auditory tube orifice as previously described, or marked reduction of the size of lymphoid tissue in and about the auditory tube orifice. Six patients not included in this series of thirty-two had a recurrent central adenoid mass associated with lymphoid hyperplasia in and about the auditory tube orifice, and conduction deafness. The central adenoid mass was removed surgically, myringotomy and spot suction performed, and roentgen therapy followed operation procedures with good results and recovery of normal hearing. These six patients are not included in the above series of thirty-two cases because it is not certain whether secondary adenoidectomy, myringotomy, and spot suction alone or operation plus roentgen therapy was responsible for the recovery of hearing. Many patients in addition to improved hearing after roentgen therapy received improvement in other symptoms. They reported fewer colds, earaches, sore throats, nasal obstruction, and a return of a clear feeling in their ears. Patients with a fluid level seen through their ear drums, and patients with dull lusterless retracted thickened ear drums regained a normal appearing ear drum after roentgen therapy.

A few case reports should be of interest:

Case 1.—A six-year-old boy (R.S.) was first seen November 29, 1950. He had had frequent attacks of otitis media and colds. His hearing was impaired even between colds. Examination revealed dull lusterless retracted ear drums, a well-performed tonsillectomy, and lymphoid hyperplasia in and about the auditory tube orifices. His audiogram returned to normal two months after roentgen therapy. His ear drums and auditory tube orifices had a normal appearance at this time also. To date, one year after treatment, his colds have been less in severity and frequency, and he has had no otitis media accompanying these colds. His hearing is normal, and his speech has been clear since roentgen therapy, according to the mother.

Case 2.—A nineteen-year-old woman (Mrs. G. W.) was first seen on August 30, 1949. She had complained of hearing difficulty for several years. Examination revealed auditory tube orifices blocked by lymphoid hyperplasia, tonsils and adenoids removed, dull retracted ear drums, negative Rinné, prolonged Schwabach, and impaired hearing by audiometric test. Only temporary improvement in hearing could be obtained by eustachian tube inflation. She was given 600r of roentgen therapy, and one month after this she happily reported that she could hear the whistle blow where she worked for the first time. Audiogram confirmed improvement in hearing. Her auditory tube orifices and ear drums returned to normal appearance, and audiogram at two months and two years after roentgen therapy showed sustained marked improvement in hearing.

Case 3.—A thirteen-year-old girl (M. M.) was first seen on August 5, 1949. She had had frequent sore throats, colds, fullness in the ears, and trouble hearing, especially in the left ear. Examination disclosed tonsils and adenoids removed, lymphoid hyperplasia in and around the auditory tube orifices especially on the left side, excessive lymphoid follicles on the posterior pharyngeal wall, and hearing impairment more marked in the left ear. One month after completion of roentgen therapy she stated that her ears felt clear. Audiogram showed improvement in hearing more so in the left ear and her auditory tube orifices appeared normal.

Case 4.—A fourteen-year-old boy (J. W.) was first seen on June 16, 1949. He had had chronic hearing impairment for two to three years, and a history of allergy. Examination disclosed allergic rhinitis, lymphoid hyperplasia in and about the auditory tube orifices, tonsils and adenoids removed, marked excess lymphoid follicles on the postpharyngeal wall, dull, retracted ear drums, and hearing impairment more marked in the left ear. Roentgen therapy was started and two weeks after the last treatment, his audiogram was normal, his ear drums and eustachian tube orifices appeared normal, and marked reduction in the size of lymphoid follicles on the postpharyngeal wall was seen. Recent conversation with the mother revealed that this boy's hearing recovery was sustained.

Case 5.—A five-year-old boy (S. P.) was first seen on November 16, 1948. This boy had had frequent attacks of otitis media with discharge, very frequent colds, and chronic hearing trouble for one to two years. His tonsils and adenoids had been removed at three years of age. Examination disclosed a red boggy nasal mucosa, red excessive lymphoid tissue in the lateral pharyngeal bands extending into and around the auditory tube orifices, dull lusterless ear drums, and hear-

ing impairment by whispered voice and audiogram. Audiogram and whispered voice showed good improvement three weeks after the last x-ray treatment, and this continued to normal hearing. The mother reported one year later that the boy was getting along much better after x-ray. His breathing was better, and he had had fewer colds and much less ear trouble. Nasopharyngoscopy one year later showed normal auditory tube orifices.

Case 6.—This case is not one of lymphoid hyperplasia, but it proves that x-ray radiation can reach the auditory tubes and nasopharynx and alleviate obstruction therein. A sixty-one-year-old woman was first seen on December 15, 1950. This woman had had blocking and trouble hearing in the left ear for nine months, chronic sore throat for six months, and recent bleeding from the left side of the nose, and weight loss. She had a characteristic odor about her. Having detected the odor of much carcinoma during my residency training at the University, I immediately suspected carcinoma of the nasopharynx. Squamous cell carcinoma around the left auditory tube orifice was confirmed by inspection and biopsy. The left ear drum showed characteristic signs of secretory otitis media with retraction, prominence of the malleus, and diffuse amber color of the drum. Deep roentgen therapy in cancerocidal doses was given before a radium plaque was inserted in the nasopharynx, and the important point is that the left ear cleared completely, and hearing returned to normal after roentgen therapy, and before the radium was inserted.

Conclusions

1. A discussion of the use of roentgen therapy in the management of conduction deafness has been given and the experience with this therapy has been reviewed.

2. Roentgen therapy has a definite and useful place in the management of deafness secondary to auditory tube obstruction from lymphoid hyperplasia.

3. No permanent harmful effects from roentgen therapy have occurred when given by an experienced radiation therapist.

4. The otolaryngologist and roentgenologist must work together in this form of therapy.

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SIMPLE PROCTOLOGIC PROCEDURES

(Continued from Page 1038)

postoperative period. Unless the primary fistulous opening is eliminated, the fistula will recur. The sphincter fibres which overlie the fistulous tract must be incised. However, if the wounds are treated properly during the healing phase, one can expect very little disability from the severed sphincter fibres.

Summary

1. The time has come when proctoscopic examinations must be performed by all physicians interested in arriving at accurate diagnoses of lesions in the rectum and lower sigmoid colon.

2. The early diagnosis and eradication of polyps in the rectum and lower sigmoid colon will solve a large part of our cancer problem.

3. A large number of troublesome lesions of the anorectal region can be treated by simple surgical procedures. Accuracy in diagnosis, plus a basic and accurate knowledge of the anatomy and physiology of the involved structures, is essential for the proper treatment of these lesions.

ANTICOAGULANTS IN CARDIOVASCULAR DISEASE

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"Thromboembolism is not a disease or a syndrome. It is a fundamental pathologic process common to a variety of disorders. It is the considered opinion of competent observers that we are today only crossing the threshold into a vast field of clinical pathology which evolves from the formation of intravascular clots."[5]

THIS STATEMENT from the most important contributor to a rapidly advancing field of clinical knowledge emphasizes the usefulness of anticoagulants over a broad spectrum. The outlook for patients suffering from such conditions as pulmonary embolism, venous thrombosis, arterial occlusion due to thrombosis or embolism, and congestive heart failure has been materially altered by the availability of these substances.

The first suggestion that intravascular clotting and the serious results thereof could be controlled came with the discovery of heparin and its introduction in 1938 in the treatment of thrombosis. With the purification of this substance to eliminate the early toxic effects due to impurities, numerous investigators established its usefulness in therapy. Meanwhile, the discovery of the first of the cumarin products at the University of Wisconsin introduced an anticoagulant which had many advantages. This progress, together with the more widespread recognition of thromboembolic phenomena, set the stage for the remarkable work with these substances which followed.

Of major importance in this therapy is the use of the anticoagulants in conditions affecting the heart. These include peripheral thromboembolic conditions, coronary occlusion with myocardial infarction, rheumatic heart disease with auricular fibrillation and embolism and congestive heart failure, conditions in which this type of treatment has been widely accepted. Peripheral vascular conditions associated with thromboembolism frequently complicate heart disease and contribute to the clinical picture as the result of lodgement of emboli originating in the heart or as the frequently unrecognized origin of emboli, especially to the lungs, occurring during the course of heart disease. Sudden peripheral arterial occlusion due to thrombosis or embolism, thrombophlebitis, and phlebothrombosis carry serious prognostic implications and should be treated with the anticoagulants both in the acute attack and prophylactically. These vascular complications occur frequently in other than cardiac conditions in which patients of older age groups must be confined to bed or similar inactivity for prolonged periods. Anticoagulant management of these conditions with its resultant marked decrease in mortality makes it necessary to search for them more diligently than has been done in the past.

In 1942 significant reports began to appear in the literature dealing with the problem of thromboembolism and the use of dicumarol in coronary thrombosis. Statistical studies concerning the significance of the problem soon followed. Wartman and Hellerstein,[9] reporting 160 cases of myocardial infarction studied at autopsy, found 38 per cent to have multiple fresh, or fresh and old infarcts. Mural thrombi were found in 34 per cent of those patients who had a single infarct and 48.5 per cent of those who had multiple attacks. These showed mortality figures for the acute attack varying considerably, from 50 per cent in early reports, to 8 per cent in some later ones. Averaging the figures on control patients in ten communications on dicumarol therapy published since 1946, the mortality is shown to be 31.1 per cent of a total of 1,180 cases. In addition to this it also became evident, after the importance of thromboembolic complications in infarction became known, that these were an important factor in prognosis. Clinically recognized secondary myocardial thrombosis during the immediate convalescence from a previous infarction occurred with varying but significant frequency. These always carried a higher mortality than the earlier ones.

Peripheral thromboembolic lesions complicating coronary thrombosis may be easily overlooked as is seen by the increasing frequency with which they are being reported, especially at autopsy. Clinically, a series assembled from the literature[2] revealed that 11.5 per cent of coronary thrombosis patients had them, while reports from autop-

Read at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

sy investigation showed an incidence of 25 to 70 per cent of such lesions. Hellerstein and Martin[3] showed that peripheral thromboembolic lesions occurred in 55 per cent of cases in which mural thrombi were demonstrated as compared with 39 per cent of those in which they were not. The difficulty of recognizing all of the thromboembolic lesions clinically is shown in the report of 200 cases by Eppinger and Kennedy[2] in which 8.3 per cent of patients with acute coronary thrombosis dying during the subacute period showed them at autopsy, but in only 4.8 per cent were they recognized clinically. Obviously the degree of clinical suspicion as well as the thoroughness of postmortem examination affect these figures materially. Peripheral thromboembolic lesions occur in the following order of frequency: lung 23.5 per cent, kidneys 14.4 per cent, spleen 8.8 per cent, extremities, 5.5 per cent.

The results of these and other studies encouraged the use of anticoagulant therapy and led to favorable reports but the numbers of cases were insufficient to warrant final conclusions. Cognizant of this, the American Heart Association established a co-operative project to study the problem and a committee consisting of investigators from sixteen leading hospitals was appointed for this purpose. In 1948, Wright, Marple and Beck[10] reported for this committee on the results obtained in the treatment with dicumarol of 1,031 patients who had coronary occlusion with myocardial infarction. This report showed a mortality of 15 per cent in dicumarol treated patients compared with 25 per cent in the control series. It also demonstrated that the greatest improvement was in those cases which showed thromboembolic complications prior to death, that the reduction in death rate was chiefly effected by control of thromboembolism. Death rates by weeks of illness were highest in the first two weeks, but still considerable in the third and fourth weeks. Greatest benefits were shown in patients over sixty years, not only in saving lives, but also in preventing serious permanent disabilities such as hemiplegia, chronic venous insufficiency, or residual myocardial damage (following myocardial infarction). Thromboembolic complications occurred in 25 per cent of control cases and 6 per cent of cases effectively treated with anticoagulants. These complications were new infarcts, extension of infarcts, pulmonary, cerebral or peripheral emboli and venous thrombosis. The results of this study have been widely accepted as justifying the conclusion that anticoagulant therapy should be given to all patients with coronary thrombosis and myocardial infarction unless specific contraindications exist.

In addition to coronary thrombosis there are two other primary heart conditions in which anticoagulant therapy is indicated. Patients having rheumatic heart disease with auricular fibrillation occasionally develop multiple peripheral emboli from mural thrombi. These patients, subject at any time to permanently crippling embolic disease, should have anticoagulant therapy with the cumarin compounds. Wright and Foley[11,12] have described a series of patients so treated and have reported their results in these cases as truly dramatic. The other condition is that of congestive heart failure in which thrombi frequently occur due to slowing of the blood stream. The results obtained by Anderson and Hull[1] and other workers indicate a definite decrease in the incidence of thromboembolic phenomena as well as a resulting decrease in mortality. This is a condition in which the anticoagulants must be used with more than ordinary caution because of the increased sensitivity to them in the presence of impaired liver function, so commonly found in congestive failure.

Contraindications to the use of anticoagulants may be listed as follows:

1. *Hypoprothrombinemia,* usually associated with liver or pancreatic disease, or intestinal diarrheal disease. These conditions are marked by a deficient synthesis of prothrombin due to an inability to use Vitamin K.
2. *Vitamin C deficiency,* animal experiments on which indicate that the effect of a given dose of dicumarol is enhanced and prolonged. Wright[5] maintains that all patients should be given Vitamin C with anticoagulant therapy.
3. *Renal insufficiency,* in which exaggerated dicumarol effects result. The reason for this effect is not clear.
4. *Blood dyscrasias,* purpura, leukemia, aplastic anemia, in which bleeding tends to occur. In polycythemia it may be used with caution.
5. *Immediate postsurgical problems,* ulcers, especially of the gastrointestinal tract, and late pregnancy, in which massive hemorrhages may occur.
6. *Subacute bacterial endocarditis,* in which the risk of hemorrhage seen in this disease may be increased.

Administration of anticoagulants in acute problems should be started with heparin the action of which is almost immediate. It must be given

parenterally, by continuous drip or intermittent administration intravenously, or by intermittent injection of an aqueous solution or a suspension in a slowly absorbed preparation as Pitkin's menstruum or as depo-heparin intramuscularly or subcutaneously. The simplest method, and most comfortable for the patient, is the intermittent intravenous injection of 50-75 mgm. of heparin every four hours. Heparin in Pitkin's menstruum may be given in average doses of 300 mgm. daily. Depo-heparin is given in doses of 200 mgm. twice daily, watching the coagulation time before each injection. If the latter exceeds twenty minutes the next dose is omitted or postponed. Objections to Pitkin's menstruums are the local pain which it usually produces and the variable effect it has on the coagulation time.

With the start of heparin, the prothrombin time is determined, and if normal, 200-300 mgm. dicumarol is given orally, followed by 100 mgm. daily until the prothrombin time reaches twice the control. The heparin is then stopped and the dicumarol continued in doses designed to keep the prothrombin activity at that level. Dicumarol acts by interfering with the synthesis of prothrombin in the liver and has the definite advantages of being cheap and orally effective. It must be remembered in judging dosage that it takes from forty-eight to seventy-two hours for it to become fully effective, and that the action persists for two to seven days after discontinuing the preparation. Also the response in individuals varies, as does the response in the same individual. Within a week the needs of the average patient can be ascertained but because of these varying factors the prothrombin time must be determined daily for a considerable period. Later, if the administration is prolonged it is usually possible to extend the intervals between prothrombin estimations. While several techniques have been recommended for determining prothrombin times, the Link-Shapiro modification of the Quick method is most widely used, expressed in seconds as compared with the control time or the percentage of prothrombin activity.

The average necessary maintenance dose is 50 mgm. daily. Occasional hyporeactors may require up to 200 mgm. daily, while hyper-reactors, sometimes seen in cases with renal or hepatic damage or chronic myocardial insufficiency, require less. Some observers have recommended larger doses two to three times weekly, but the use of smaller daily doses is more widely accepted. Where the prothrombin time fluctuates erratically, divided doses of dicumarol or the use of one quart of milk daily has been recommended to increase stability. Therapy is continued for 20 to thirty days after the thromboembolic episode with the object of keeping the prothrombin time at two to two and a half times the control as recommended by Nichol.[6] The method of administration here outlined is applicable as well to any condition in which prompt anticoagulant effect is desired.

The anticoagulants have been non-toxic except for the hemorrhagic complications which with increasing experience have presented no risk that is unjustified. These manifestations such as epistaxis, minor hemoptysis, bruising and the appearance of erythrocytes in the urine have been infrequent and usually unimportant. The latter, if watched for, may foretell the occurrence of the only really important major complication, hematuria. Several occurrences of this have been seen, but in instances where lapses in observation occurred and where symptoms pointing to probable renal involvement should have been a warning to stop therapy. These consisted of low back and groin pain of aching type, occurring several days before gross hematuria and renal colic appeared. While this caused considerable discomfort for several days, complete healing with no sign of residual renal damage occurred. Serious hemorrhage, then, is usually a sign of poor management, or the overlooking of ulcerative lesions, usually gastrointestinal, from which bleeding occurred.

With the onset of hemorrhage, the anticoagulant must be stopped. If not serious, the condition will soon correct itself. If marked, transfusion should be instituted, replenishing the patient's prothrombin. The latter is used up rather quickly and the transfusion should be repeated at four- to six-hour intervals until the prothrombin time is decreased. At the same time Vitamin K is injected intravenously in the form of Menadione, Synkavite, Hykinone or similar preparation, in doses of 60-72 mgm. every four hours until the prothrombin time returns to normal. Even with these measures considerable time, several days, may elapse before the condition is corrected. The Vitamin K preparations do not lessen the hypoprothrombinemia but counteract it and control the bleeding. Recent studies[4] indicate that

Vitamin K_1 oxide acts much more rapidly in restoring prothrombin times to safe levels.

Aware of the importance of recurring coronary thrombosis after an attack, Nichol and Borg[7] set out to determine the feasibilty of long-term ambulatory dicumarol therapy following an acute attack and presented a preliminary report on their results in 1950. All patients intelligent enough to understand and co-operate with the program were continued on dicumarol therapy with the object of keeping the prothrombin time at a level approximately twice the control, after the aims of the program had been explained to them. They were told to be on the alert for any untoward symptoms or evidences of bleeding, on the occurrence of which they were to discontinue the drug. They were also instructed to stop the drug during the occurrence of any gastrointestinal disorder on the theory that undetected liver disturbance might be present. Prothrombin times were checked at intervals up to two weeks. These results indicated that the method is a feasible one. Criticism that it would tend to make patients too heart-conscious and provoke and increase cardiac neurosis has seemed unjustified. In fact it seems to have been a reassuring program to most of them and there have been no serious problems of that type. The patients seem willing and anxious to partake in a program designed to give them protection against future trouble. Since the 1950 report, the number of patients in this study has been considerably augmented and continuance of the program has been encouraged.

A report on subsequent experience was presented before the recent meeting of the American Heart Association. In this, the following data on 224 patients which are included in the joint program and have been on anticoagulant treatment for two to fifty-nine months were presented. A hundred and twenty-six patients have continued therapy since its inception, and sixty-four patients have discontinued treatment voluntarily. Peripheral thromboembolic phenomena have not been observed in this group.

Hemorrhagic complications have occurred in ninety-four of the entire group. Fifty-three of these were minor such as epistaxis, purpura, hemoptysis, bleeding gums. Forty-one were classed as major hemorrhages, notably gross hematuria in twenty-two patients, gastrointestinal hemorrhage in four patients and hematoma in five patients. All of these recovered without sequelae. With increased experience in management and improved alerting of patients for the early appearances of complications, the latter are now relatively unimportant. No major hemorrhages have been observed in this writer's experience during the past three years.

Thirty-four patients have died while under treatment. Autopsies were performed on fifteen of these, in which four showed fresh infarction, five showed subendocardial fibrosis, and six showed old healed infarcts. Among those not examined postmortem were ten patients who died suddenly, two who died within 48 hours after an attack of protracted coronary insufficiency (not proved infarction), five who died from congestive heart failure, and two from probable cerebrovascular accidents.

It will take a considerably extended and prolonged study of this type to justify drawing significant conclusions. Until better studies of the expected course in a series of first infarctions are available, the value of this procedure must be regarded conservatively. The high percentage of survivors, however, together with the low percentage of recurrence of coronary thrombosis in this series as compared with the prognosis in patients not treated with long-term anticoagulants, suggests the desirability of this type of management of patients with myocardial infarction.

When it is recognized that there is much about intravascular clotting and anticoagulants that is not understood, it is not surprising that failures and even deaths with this treatment occasionally result. Analysis of these shows that usually the blame must be put on management, due to: (1) delay in the institution of therapy; (2) inadequate prothrombin blood levels; or (3) premature discontinuance of medication. If these factors can be controlled, failures will be few, yet there will be found isolated rare instances in which thromboembolic phenomena may occur in patients supposedly well handled.

Since the discovery of dicumarol with the recognition that it is not the perfect anticoagulant, search has been, is being, and will continue to be made for a more satisfactory product. To date two preparations have been made available to the profession, both satisfactory anticoagulants. Tromexan has the advantage of reaching its peak activity more quickly, in twelve to eighteen hours, with the action of a dose subsiding in about forty-eight to sixty hours. Maintenance dose varies

from 600-900 mgm. daily. Cyclocumarol recently has become available with more rapid onset of effect than dicumarol and more prolonged action. These have been regarded as advantages by some. The average initial dose is 100-200 mgm., with maintenance doses averaging 25 mgm. It is difficult to recognize important advantages over dicumarol in the later products. Serious hemorrhagic complications should not occur in well managed patients. Where they do, the same procedures for treatment apply for all preparations. On the other hand, the cheapness of dicumarol has much to recommend it, especially if the substance is used over a long period of time, and if the physician is well versed in its action it will be found to be a satisfactory product.

Conclusion

1. The anticoagulants have opened an important new field of treatment in heart disease.

2. Mortality and morbidity in coronary thrombosis, congestive heart failure and rheumatic heart disease complicated by multiple emboli have been markedly improved.

3. Long-term anticoagulant therapy has been proved feasible and gives promise of considerable value in decreasing morbidity and mortality in patients who have recovered from myocardial infarction.

4. Anticoagulants are not essentially toxic in themselves but poorly managed use of them can lead to hemorrhagic complications.

5. The use of anticoagulants requires the utmost of vigilance and intelligent knowledge as to their action and no physician who is unwilling to accept this should assume the responsibility of their use.

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NEW DRUGS IN THE TREATMENT OF HYPERTENSION

(Continued from Page 1024)

Because undesirable reactions can occur, it would seem advisable to institute this program of treatment only for the more severe forms of hypertensive vascular disease and only if the program can be started in a hospital under careful supervision of a physician and continued under the close supervision of the physician.

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FUNCTIONAL UTERINE BLEEDING

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ABNORMAL UTERINE bleeding has been discussed many ways. I should like to restrict the subject to problems arising in the sexually active woman and related to abnormalities in the physiology of the menstrual cycle.

The physiology of the normal cycle must be considered before approaching the abnormal. In brief, the cycle must be considered as two phases ending either in pregnancy or menstruation. The first, or proliferative phase, is the result of the estrogenic hormones secreted by the developing follicle. During this portion of the cycle, the cells of the glands and stroma increase in number. This results in a thickened endometrium containing fairly straight glands showing little secretory activity. The luminal borders are smooth, the nuclei are usually more or less centrally located and the amount of cytoplasm is minimal. Following ovulation, the endometrium is affected in a striking fashion by progesterone, the hormone produced by the corpus luteum. Estrogenic hormones are maintained at approximately the same level throughout the entire cycle. The active growth or proliferation seen in the first phase now ceases and is replaced by physiological changes in the stroma and glands in preparation for nidation. The second, or secretory phase, is recognized histologically by the huge increase of cell size in both stroma and gland. The glandular cells are swollen and begin active secretion. The increase in cell size causes the gland to bend and turn in a tortuous fashion, straightening out only near the surface of the endometrium where the stromal cells are prominent. Should pregnancy result, secretory activity is accentuated. Lacking this, the endometrium is cast off over a period of three or four days. The entire cycle is then repeated. The regular shedding of endometrium is the result of estrogen and progesterone withdrawal.

The rhythmic pattern of the menstrual cycle can be interrupted during either phase, resulting in abnormal uterine bleeding. Bleeding of this nature, in other words functional bleeding, can be accurately diagnosed histologically and explained hormonologically.

Hyperplasia of the endometrium, the more frequently occuring lesion, is related to the first, or proliferative phase and is the result of continued estrogenic hormone effect uninterrupted by the effect of progesterone. The basic cause is the failure of ovulation due to an unexplained breakdown in the normal pituitary-ovarian relationship. It is not known why the pituitary gland suddenly fails to bring about ovulation and luteinization. Curiously enough, one cannot successfully produce ovulation and luteinization by the administration of anterior pituitary substances in human beings. This explains the unsuccessful results in the use of gonadotrophic hormones in the treatment of hyperplasia.

The greatest incidence of hyperplasia is in the young girl and the woman approaching the menopause. The degree of disability varies widely. Some patients describe long intervals of inactivity followed by uterine bleeding which may be prolonged, heavy, or both. On the other hand, the bleeding phase may be almost constant with only a few days during which the patient will be free of blood loss. The usual symptoms are those resulting from acute or chronic blood loss. The findings on physical examination are not unusual, although some authors have noted a rather high incidence of enlarged, cystic ovaries.

While the history is often very suggestive, it is unwise to begin definitive therapy until the diagnosis has been established histologically. Not infrequently, curettage will reveal some other pathological finding uninfluenced by medical therapy. These lesions vary from malignancy involving the endometrium or the cervical canal to the lesser important incomplete abortion or polyp. Once the diagnosis is established by curettage, one is justified in following the course of the disease by the use of the endometrial biopsy. In the older patient, do not forget the danger of carcinoma developing even though a diagnosis of hyperplasia has been made previously by curettage. Thus, if too great a lapse of time exists between the original curettage and the recurrence of irregular bleeding, do not hesitate to recurette.

Read at the annual meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 27, 1952.

The management of hyperplasia can be roughly divided into two categories. First, efforts are directed toward the control of bleeding. Second, attempts are made to re-establish normal, regularly occurring, menstrual periods. Profuse bleeding is best controlled by curettage. This should be the method where no previous histological diagnosis has been made, or when the bleeding is of proportions sufficient to produce marked anemia or shock. Patients previously curetted who are not bleeding to an alarming degree may be treated hormonologically. Just about every individual interested in hyperplasia has a method which he believes superior. Since the methods vary widely, it is apparent that the perfect method is not available. Bleeding can be controlled with testosterone, stilbestrol, the true estrogens, and with progesterone. Some methods employ combinations of two or more hormones with apparent success. It is not my purpose to outline the various procedures, but instead to present one approach to the problem which is based upon the physiology of the menstrual cycle. It is admitted that no single method will be successful in all cases, therefore anyone handling hyperplasia is justified in trying different methods when the initial effort is without success.

Since the bleeding phase in hyperplasia is the result of estrogen withdrawal, the re-establishment of available estrogenic substances should have a healing effect. This is true. Large doses of estrogens will cause cessation of bleeding. This can be done by the oral, intramuscular, or intravenous administration of estrogens. The latter may well produce a quicker response, but my own personal experience is limited. The following routine has proven adequate in most cases. The patient is given 40,000 International Units of crystalline estrogenic substance intramuscularly. This is followed by the oral administration of five milligrams of conjugated estrogens daily for five days. This usually stops the bleeding. On the third day of therapy, 100 mg. of progesterone is given intramuscularly. Five to seven days after the administration of progesterone, the patient will bleed again for about the same length of time associated with a normal menstrual period. We have produced a secretory endometrium which is shed after the withdrawal of the hormone therapy. Hormone therapy following this physiological curettage is directed toward the re-establishment of rhythmic bleeding. Abnormal findings, such as secondary anemia, a low metabolic rate, and obesity must also be corrected.

The third day of the artificially created menstrual bleeding marks the starting point of treatment each month. Thereafter the patient is given 2.5 milligrams of conjugated estrogens orally each day for three weeks. On the twenty-first day of the artificially created cycle the patient is given 100 mg. of progesterone intramuscularly or is given 50 mg. of progesterone intramuscularly every other day for a total of three doses. Both methods are satisfactory. A larger single dose has the advantage of requiring only one visit to the office by the patient during the treatment period. It is, however, considerably more painful than the smaller dose. If the treatment is successful, the patient should bleed approximately one week after the administration of the progesterone. This cyclical therapy should be repeated over a period of three months. Treatment is then discontinued to observe possible resumption of menstrual periods in the normal fashion. The treatment is not intended to be a direct stimulation upon the faulty pituitary gland and ovary. Actually it is directed toward the end organ, the endometrium. However, it is suggested that re-establishment of rhythmic bleeding has a beneficial effect upon the ovary and pituitary gland which results in the re-establishment of ovulation. The success of the treatment cannot be accurately explained. It does avoid the use of substances, such as testosterone and stilbestrol, which may have undesirable side effects.

The described method of treatment may be repeated, particularly in the young girl or woman desirous of further pregnancies. Unsuccessful hormonal management of the young woman who has obtained her desired family may sometimes justify hysterectomy. The older woman near the menopause who has repeated episodes of severe bleeding should have the already failing ovarian function eliminated by the simple application of a sterilizing dose of x-ray to the pelvis.

The young girl must be handled conservatively. She must be given every opportunity to re-establish normal ovarian function. The use of surgery in these children must be restricted to curettage, even if it be used repeatedly. Eventually, these patients establish regular menses or, as has occurred in a few instances, amenorrhea.

The presence of hyperplasia in the prepubertal

or post menopausal patient must be investigated thoroughly for the possible presence of an estrogen-producing tumor. This, however, is not within the scope of the present paper.

Functional bleeding may be caused by a less widely known condition called irregular shedding. Here the abnormality is associated with the secretory phase of the menstrual cycle. The underlying cause of irregular shedding is not as well understood as in hyperplasia. There is evidence to show that there is an incomplete withdrawal of hormones at the time of menstruation. Instead of a prompt decrease of progesterone prior to bleeding, the quantitative withdrawal is gradual over several days. This prevents a complete disintegration of the endometrium, resulting in an irregular shedding of the surface and a retention of secretory endometrium. Because the previously functioning endometrium is partially retained, complete healing of the surface cannot occur. As a result of this pathological retention, the menstrual bleeding is prolonged. Diagnosis of the condition is possible only by the use of a properly timed curettage. One must do the operation after the fourth day of bleeding. It is useless to curette the patient after bleeding has stopped. Tissue properly obtained will demonstrate a characteristic histological picture in which the stroma appears contracted and darkly stained. The endometrial stroma has the appearance of breaking into small fragments. The glands retain the appearance of the secretory phase, but are usually collapsed and assume a starlike shape. Little cytoplasm will be evident, indicating a state of exhausted function.

The diagnosis of irregular shedding is suggested by a history of prolonged bleeding which occurs rhythmically and at the expected time of the menstrual period. The patients are predominately in the older age group. Younger women may exhibit this disease not infrequently following a pregnancy. One could attempt biological assays to establish diagnosis, but this is impractical. Curettage, properly timed, is the most effective means of diagnosis and treatment.

The treatment of irregular shedding by medical means has not been successful. This is not important, however, since a very high percentage of patients are cured by curettage alone. In younger women, curettage is usually followed by normal periods. In the older age group, the curettage may be followed by the resumption of normal bleeding or by the cessation of periods completely. In some instances the condition is unaffected by the curettage. Since irregular shedding is related to ovarian failure, function may be completely eliminated by x-ray sterilization. In the younger age group, the administration of large doses of estrogens after several days bleeding has been used with some success. Occasionally very severe cases require repeated curettage or hysterectomy.

In summary, specific methods for the management of functional uterine bleeding have been presented. Emphasis is placed upon the need for histological diagnosis before a definite hormone program is started. The therapy recommended is based upon the use of hormones which have no untoward side effects and are physiologically sound.

ISONICOTINIC ACID HYDRAZIDE

Isonicotinic acid hydrazide, the most recent development in the therapeutics of tuberculosis, if it proves to have a comparable effect in humans as has been demonstrated in animals—will have its important place in the treatment of tuberculosis, but also its limitations. It was two or more years after streptomycin began to play an important role before resection of diseased pulmonary tissue began to have its effect in the treatment of tuberculosis.

It is more than likely that isonicotinic acid hydrazide will have an effect in the treatment of tuberculosis that may be even greater than that of streptomycin, but up to this point clinical evidence is not available to substantiate assumptions based on animal experimentation. Basically the success of treatment now depends upon bed rest, good nursing care, graduated exercise, combined with a judicious selection of appropriate therapeutic measures, both surgical and medical, under close medical supervision in tuberculosis hospitals.—PAUL S. PHELPS, M.D., and REGINALD C. EDSON, M.D., *Connecticut State Medical Journal*, May, 1952.

President's Letter

A PAUSE FOR THANKS

Giving thanks in America is often merely a ritual which we observe annually at Thanksgiving time. Yet, the typical American Thanksgiving dinner—with turkey, dressing, cranberries, squash, mashed potatoes, rich gravy, sweet potatoes, pumpkin pie with whipped cream, and all the other trimmings—is symbolic of the land of plenty which America is today.

And, it is fitting, too, that America was the scene of the first Thanksgiving Day. But that first official day for returning thanks was vastly different from the Thanksgiving we observe today. The Pilgrims had survived a long hard year of striving to stay alive and they were genuinely grateful for all they had. Today, we have no comparable hardships to endure. Possibly, our main difficulty is sparing enough money from other luxuries to pay for our huge feast. And yet, many of us are not genuinely thankful. We generally are a nation which takes its blessings for granted.

Some may argue that this is one of our blessings—the privilege of taking our blessings for granted. As logical and true as that may appear, it is a complacent way to look at things. Merely to take things for granted admits a willingness to accept as ours the very things for which others worked and sacrificed.

We, as doctors, can give thanks for a multitude of things. We have the supreme privilege of serving our fellow men. We can be thankful for the good fortune of being educated to the profession of healing and of the ability to aid others to recover from illness, thus affording them reason to render thanks. Ours is a gratifying task.

As doctors, we must be thankful that our profession is unshackled. We can practice medicine with a maximum of freedom. We have access to the latest and best information which is readily adaptable for use for the good of others.

We can be thankful not only as a profession but as individuals as well. As Americans our list of blessings is long and varied. As individual Americans, we can still count the famed freedoms as our personal blessings. We still have the right of life, liberty, the pursuit of happiness, freedom of speech, press, religion, the right of assembly, privacy, due process of law and the privilege of casting votes for those we wish to have represent us.

With such a rich heritage the answer to the question, "Who has more to be thankful for than Americans?" must surely be "No one!" In pausing to give thanks for our many material gifts, let us ask that spiritual strength and blessings be granted us in equally abundant measure.

Roger L. J. Kennedy

President, Minnesota State Medical Association

Editorial

CARL B. DRAKE, M.D., *Editor;* GEORGE EARL, M.D., HENRY L. ULRICH, M.D., *Associate Editors*

POLIOMYELITIS IN MINNESOTA, 1952

THROUGH October 15, 1952, 3,117 cases poliomyelitis with 151 deaths in Minnesota residents had been reported to the State Health Department with an additional 169 cases and sixteen deaths in nonresidents. The percentage of fatal cases, in residents (4.8 per cent) is the lowest of any recent year, except 1950, when 4.1 per cent of patients died. The number of cases in 1952 exceeds that of any previously reported year, although more deaths were reported in 1946 and 1910.

This year's cases include 1,705 males, 55 per cent of the total, and 1,412 females, 45 per cent of the total. This sex distribution is the same as in recent years. Fatal cases include 88 males (58 per cent) and 63 females (42 per cent). Sixty-five per cent of the cases and 47 per cent of the deaths reported occurred in children under fifteen years of age, confirming the impression that poliomyelitis is a childhood disease primarily, and that in general the majority of adults are immune, probably as a result of unrecognized childhood infection. A fatal outcome is more likely, however, in adults who do develop the disease; 35 per cent of the cases and 53 per cent of the deaths were in persons fifteen years of age and over.

Analysis of about 2,000 of this year's reported cases, as to type of involvement, indicates that 25.8 per cent of these cases were of the bulbar type; 21.5 per cent, spinal paralytic; 52.7 per cent, nonparalytic. These percentages may not be greatly different from those of 1946, 1948, and 1949, other recent epidemic years, when finally completed.

Cases of poliomyelitis this year have been distributed widely and generally throughout the entire state, with some apparent sparing of the southwest corner where a winter outbreak was prevalent in December of 1951, and January, 1952. The State total of cases is the cumulation of all the local epidemics that flare up in various communities, and the duration and final extent of the statewide problem depends somewhat on the timing of these local outbreaks. In general, six weeks of mounting reports precede the week of peak numbers, and at least nine weeks of more slowly dropping reports follow. Thus the peak week of cases in 1946, when Minneapolis was heavily involved early in the summer, was the week ending August 17; in 1948, September 18; in 1949, August 27, and in 1952, the week ending September 13. Since the peak week this year, over 1,400 additional cases have been reported, as a result of involvement of practically all areas of the State

The chief problems this year have been to find sufficient nurses to staff the facilities required to handle the rush of cases. National resources were committed to other states prior to Minnesota's need. Progress was made in utilizing more

MINNESOTA DEPARTMENT OF HEALTH—SECTION OF PREVENTABLE DISEASES
POLIOMYELITIS

Cases Reported in Minnesota Residents According to Type

Type	1946	1948	1949	1952 (thru Oct. 15)
Paralytic	63.3%	49.2%	51.3%	47.3%
Bulbar	16.7	19.8	18.5	25.8
Spinal	46.6	29.4	32.8	21.5
Nonparalytic	28.5	49.0	45.2	52.7
Unknown	8.2	1.8	3.5	

(Above figures represent only about 2,000 cases in which type is known to date.)

MINNESOTA DEPARTMENT OF HEALTH—SECTION OF PREVENTABLE DISEASES
POLIOMYELITIS

Cases, Deaths, and Rates per 100,000 Population 1946-Oct. 15, 1952

Year	Cases	Case Rate per 100,000 pop.	Deaths	Death Rate per 100,000 pop.
1946	2,881	102.3	226	8.0
1947	201	6.9	13	0.5
1948	1,387	47.2	110	2.7
1949	1,715	57.6	111	3.7
1950	502	16.9	21	0.7
1951	511	16.9	31	1.0
1952 (to Oct. 15)	3,117	103.3	151	5.0

local facilities and opening up of private and other large hospitals in the Twin Cities for care of convalescent patients. Exaggerated fear on the part of the general public continues to be a real problem.

Many reports have come in of atypical illness occurring in communities at the same time cases of paralytic poliomyelitis have appeared and likewise in the absence of recognized polio. Some of these outbreaks have resembled those reported in other states where Coxsackie viruses have been demonstrated in persons with herpangina, pleurodynia, and nonparalytic neuromuscular complaints. There is great need for the provision of adequate resources to permit proper laboratory story of these outbreaks, using the steadily increasing knowledge of viruses that now exists.

D.S.L.

ANTABUSE® AND ALCOHOLISM

ANTABUSE® is the trade name of Ayerst, McKenna, and Harrison, Ltd., for its brand of tetraethylthiuram disulfide. It is offered in the treatment of alcoholism. The drug, when taken by mouth, delays the breaking down of alcohol in the blood, and when alcohol in any form is taken illness, sometimes violent in nature, results. The larger the dose of the drug taken, the more violent the reaction after imbibing alcohol in any form, and the more alcohol consumed, the greater the reaction. Illness on taking a drink is experienced as long as seven or eight days after a single dose of 1.5 grains of the drug. Also, the patient should not be given the drug until a period of two weeks has elapsed since he has had a drink. Dosages should be kept low—at 0.5 gm. or less, daily, for the first two or three weeks and at 0.25 gm. or less as a maintenance dose. It should also be remembered that individuals react differently to drugs—Antabuse® included.

The symptoms produced on taking a drink following the administration of Antabuse® are largely cardiovascular and consist of flushing, sweating, palpitation, dyspnea, hyperventilation, tachycardia, fall of blood pressure, nausea and vomiting. Usually, drowsiness ensuses with complete recovery following sleep.

It is obvious that the drug should not be given in the presence of other illnesses such as diabetes mellitus, myocardial weakness, coronary disease, pregnancy, goiter, epilepsy, cirrhosis of the liver or nephritis. Also, it should not be given to one over fifty years of age. As the action of barbiturates is aggravated by Antabuse,® they should not be given concomitantly.

How extensively Antabuse® is used, we do not know. We do know that it should be used only as an adjunct in the treatment of alcoholism and not as a specific for a certain disease. It should also be used with caution and only by the informed.

The other phases of treatment of alcoholism, such as hospitalization, psychiatric assistance and the treatment of co-existing disease, should not be neglected.

CORTISONE AND CORTICOTROPIN

Policy for Administration in Welfare-Sponsored Medical Care

AT a recent meeting of the medical advisory board of the State of Minnesota Division of Social Welfare, a revision of the policy concerning the use of cortisone and of corticotropin (ACTH) was discussed. With increasing medical experience in employing these hormones, and with increasing availability of the preparations, an attempt has been made by the medical advisory board to evaluate and facilitate their use when necessary by recipients of welfare-sponsored medical care.

Cognizance has been taken of the fact that this group of patients includes many elderly people who are recipients of old-age assistance. Likewise there are included other patients having diseases which might make the use of cortisone or corticotropin hazardous. One giving guidance in selecting patients for hormone therapy should first consider those diseases in which such therapy is contraindicated or in which if such therapy is undertaken it is done at an increased risk of a varying degree. Such diseases include tuberculosis, syphilis, latent or frank psychosis, severe psychoneurosis, peptic ulcer, hypertension, congestive heart failure, nephritis, thrombophlebitis, diabetes mellitus, pyogenic infections, pregnancy, convulsive disorders (exclusive of idiopathic hypoglycemia) and severe osteoporosis.

In many diseases the use of cortisone and of corticotropin has been shown to be of value. The medical advisory board has reviewed these diseases with respect to treatment by these hormones as a background for the policy it is here recommending.

Bronchial Asthma.—Patients having bronchial asthma may experience transitory benefit from cortisone or from corticotropin. The use of these

hormones is but an adjunct to other established procedures in the management of this disease. The use of these substances is best indicated in the critically ill asthmatic patient or in one seriously ill and who is failing to respond to more conservative forms of therapy. It is doubtful if the use of these hormones is justified in most patients having other allergic diseases such as seasonal hay fever, uncomplicated vasomotor rhinitis, or less severe urticaria.

Rheumatic Fever.—The effect of cortisone and of corticotropin on the course of acute rheumatic fever has been repeatedly demonstrated. Prolonged studies will be necessary, however, before the influence of these hormones on the development and course of rheumatic heart disease can be determined. Certain studies would suggest that there is a favorable influence on acute rheumatic carditis following such therapy. It would appear that cortisone and corticotropin have no influence on rheumatic heart disease sustained in previous bouts of rheumatic fever, or on damage sustained in a given course of rheumatic fever prior to the institution of hormone therapy. With our present understanding, it would appear that the use of these hormones is well justified in many instances of the acute phase of rheumatic fever.

Rheumatoid Arthritis.—Rheumatoid arthritis is characterized by a course which varies in its extent, duration and severity. Conservative measures of therapy including physical medicine, general supportive measures, rest and certain specialized forms of treatment (for example, vaccines, fever therapy, gold-salt therapy) permit favorable control of the course of the disease in many instances. The use of cortisone and corticotropin may be considered only in those patients in whom the active phase of the disease continues to be progressive despite such treatment. Even in these instances cortisone and corticotropin will be of greatest value as a supplement to, rather than as a substitute for, basic conservative measures. Beneficial effects from hormone therapy are usually limited to the duration of their administration and a varying but usually relatively short period thereafter. Only limited if any beneficial results are to be anticipated in the treatment of structural joint changes already present as the result of previous articular inflammation. These hormones will not effect a repair of extensive joint damage once such has developed.

Osteoarthritis.—The value of cortisone and of corticotropin has yet to be established in the management of osteoarthritis, that type of degenerative joint disease constituting the vast majority of instances of so-called arthritis in patients past middle age. It would appear advisable to defer for the present the acceptance of such patients for therapy.

Dermatologic Diseases.—In certain severe dermatologic diseases and in systemic diseases commonly exhibiting prominent dermatologic manifestations, the use of cortisone and corticotropin is of value. These include the acute systemic forms of lupus erythematosus and pemphigus. Those drug eruptions and systemic reactions, especially that group occurring as an urticarial or sensitization reaction following use of antibiotics or serums, may necessitate the employment of hormone therapy if more conservative types of treatment prove ineffectual. Patients having refractory noninfectious erythema multiforme or acute severe generalizing dermatitis venenata may require the use of hormonal therapy when failing to respond to more conservative management. Under careful management the use of these hormones may be indicated in patients having extensive and severe eczema or exfoliative dermatitis which has failed to respond to usual forms of therapy.

Ophthalmologic Diseases.—Patients having certain eye diseases are helped by therapy with cortisone or corticotropin. Cortisone may be administered topically; cortisone and corticotropin may need to be administered systemically. A list of eye diseases wherein hormones may be employed with success appears in a later section.

Burns.—The use of cortisone and of corticotropin in extensive and severe burns is of particular value in the shock phase of this type of injury.

Addison's Disease.—Cortisone has been demonstrated to be effective as an adjunct in replacement therapy in patients having Addison's disease. Adrenal cortical insufficiency occurring as a part of panhypopituitarism likewise may require adrenal replacement therapy in which cortisone is useful. The employment of cortisone in replacement therapy necessitates the use of far smaller doses than those commonly employed in the treatment of other diseases influenced by this hormone.

Comment

In view of the demonstrated value of cortisone and of corticotropin in the treatment of certain patients having the foregoing diseases, the medical advisory board of the State of Minnesota Division of Social Welfare has considered it advisable to recommend to the Division of Social Welfare an extension of its policy concerning the use of these hormones. Patients who otherwise qualify for medical benefits at public expense in accordance with the Statutes of the State of Minnesota

may now be eligible for treatment with cortisone or corticotropin when necessary according to the outline to follow.

In determining this outline for guidance in acceptance of responsibility in payment for cortisone and corticotropin, certain conditioning considerations have been delineated.

Certain diseases, by virtue of their rapid course, necessitate early employment of the hormones without the delays incident to securing authorization for payment for these substances. In such instances as later defined, a physician may start therapy and at that time solicit authorization for its expense from the Medical Director of the Division of Social Welfare. Prompt action will be taken on such a request. In any event, in such cases financial responsibility for the first three days of hormone treatment will be assumed by the Division of Social Welfare.

In certain other diseases not presenting an indication for the emergency use of cortisone or of corticotropin, authorization for the use of hormones at public expense should be secured in advance.

When the disease in question is one wherein a satisfactory therapeutic response may be anticipated following topical use of cortisone, relatively small amounts of the hormone are required. Illustrative of such diseases is a group of diseases of the eyes. In such instances prior authorization for the assumption of financial responsibility by the Medical Director of the Division of Social Welfare need not be obtained.

This outline, determined by physicians practicing in various sections of the state, appears to be a current equitable guide for use in a difficult problem. It is recognized that with further experience, changes in this proposed program may become necessary.

1. *Conditions wherein systemic cortisone or corticotropin therapy may be started without prior authorization for its expense,* but concerning which notification should be sent immediately to the Medical Director of the Division of Social Welfare. Liability for the cost of hormone therapy employed cannot extend beyond three days without such authorization.

(1) Status asthmaticus
(2) Acute rheumatic fever with or without associated carditis
(3) Extensive burns
(4) Systemic crises of disseminated lupus erythematosus
(5) Serum sickness (severe)
(6) Drug reactions (severe, of urticarial or sensitization type)
(7) Erythema multiforme (severe, of noninfectious type)
(8) Dermatitis venenata (acute, severe, generalized)
(9) Exfoliative dermatitis
(10) Periarteritis nodosa
(11) Pemphigus
(12) Ocular diseases which because of severity or lack of response to local treatment may require the systemic administration of hormones (for example, sympathetic ophthalmitis, acute nongranulomatous uveitis, chemical and thermal burns, posterior uveitis, retrolental fibroplasia, scleritis, acute focal choroiditis, interstitial keratitis, and late vernal conjunctivitis)

2. *Conditions wherein the liability for the expense of cortisone or corticotropin therapy will be assumed only following authorization* by the Medical Director of the Division of Social Welfare. Liability for expense of therapy cannot be assumed unless prior authorization is granted.

(1) Severe progressive rheumatoid arthritis
(2) Rheumatoid spondylitis deformans
(3) Psoriatic arthritis
(4) Nontropical sprue
(5) Idiopathic hypoglycemia with convulsive disorder
(6) Sarcoidosis
(7) Addison's disease*
(8) Panhypopituitarism
(9) Other diseases for which hormone therapy is currently being used but for which other forms of therapy permit satisfactory treatment

3. *Conditions wherein liability for the expense of cortisone employed topically will be assumed* by the Medical Director of the Division of Social Welfare. Eye diseases wherein cortisone topically administered may be expected to be of value include the following.

(1) Sympathetic ophthalmitis
(2) Acute nongranulomatous uveitis
(3) Postoperative uveitis
(4) Chemical burns of the eye
(5) Thermal burns of the eye
(6) Episcleritis
(7) Scleritis
(8) Interstitial keratitis
(9) Keratoplasty (postoperatively)
(10) Recurrent corneal ulcer
(11) Allergic blepharitis and blepharoconjunctivitis
(12) Vernal catarrh (early stage)
(13) Phlyctenular keratoconjunctivitis
(14) Acne rosacea keratitis
(15) Endophthalmitis phacoanaphylactica

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*In this disease only cortisone should be employed.

Medical Economics

Edited by the Committee on Medical Economics
of the
Minnesota State Medical Association
George Earl, M.D., Chairman

WMA WOULD LIMIT SOCIAL SECURITY

A sound and sensible attitude toward social security schemes on a broad basis is presented in a recent statement by the World Medical Association. The international medical group states that "Doctors are perturbed by possible unfavorable effects of Social Security schemes on individual men and women. While they recognize that society has an obligation to help those who through nature, nurture, accident, disease and environment are handicapped in the struggle to survive, they fear the demoralizing effects of state paternalism exercised on adults."

Stating that a powerful factor in promoting good health and quick recovery from illness is a sense of personal responsibility, the WMA feels that any scheme which tends to decrease this personal responsibility is not a sound one. "The more the State does in this direction (free medical services), the less is the individual sense of obligation and responsibility," the statement says.

Lays Down Principles

The World Medical Association then goes on to recommend that:

1. When Social Security schemes are necessary, they should be developed in the closest collaboration with the medical profession. Such schemes should take into account the psychological effects on the beneficiaries of increased dependency and diminished responsibility.
2. The fundamental aim of a Social Security scheme should be to raise the individual to a level at which he can help himself. From this, it follows that:
3. Any Social Security scheme should contain elements that encourage self-reliance and a sense of personal responsibility, and that;
4. Any Social Security scheme should stress the obligation of the individual to make at least part of his contribution directly to the functioning and costs of the scheme.

The WMA stipulates that whenever medical care is provided as part of social security, the following principles should govern it:

1. Freedom of choice of physician by the patient. Liberty of physician to choose patient except in cases of urgency or hunanitarianism.
2. No intervention of third party between physician and patient.
3. Where medical service is to be submitted to control, this control should be exercised by physicians.
4. Freedom of choice of hospital by patient.
5. Freedom of the physician to choose the location and type of his practice.
6. No restriction of medication or mode of treatment by physician except in case of abuse.
7. Appropriate representation of medical profession in every official body dealing with medical care.
8. It is not in the public interest that physicians should be full-time salaried servants of the government or social security bodies.
9. Remuneration of medical services ought not to depend directly on the financial condition of the insurance organization.
10. Any social security or insurance plan must be open to the participation of any licensed physician, and no physician should be compelled to participate if he does not wish to do so.
11. Compulsory health insurance plans should cover only those persons who are unable to make their own arrangements for medical care.
12. There shall be no exploitation of the physician, the physician's services or the public by any person or organization.

NEW REPORT ISSUED ON MORTALITY TRENDS

The Bureau of Medical Economic Research of the American Medical Association has recently issued a new comprehensive report on mortality trends in the United States since 1900. Although the report is presented with the bureau's usual intensive and inclusive study of facts and figures, it offers a clear and concise picture of the mortality situation in this country. Dr. Frank G. Dickinson, bureau director, states in the report:

"The decline in the crude mortality rate from 17.2 deaths per 1,000 population in 1900 to 9.7 in 1949 understates the health progress of the last half century. While the population has doubled, the number of persons over sixty-five has quadrupled in this period."

Speaking editorially, *The Journal of the American Medical Association* said of this report:

"Although the emphasis of the bulletin is on causes of death, the numerous charts and tables combined with the penetrating analysis of mortality trends provide physicians and other students of vital statistics with a clear-cut analysis of the spectacular reductions in mortality during the past half century."

Explaining the increase in life expectancy further, the editorial stated:

"A small portion of the twenty-year increase in life expectancy at birth resulted from mortality gains at the higher ages; for example, the 22 per cent drop in mortality at ages sixty-five to seventy-four accounted for 2 per cent of the increase. . . . Life expectancy at any age reflects the mortality rates among older persons in a particular calendar year. What those mortality rates will be ten or twenty years from now cannot be discerned from any current table of life expectancy values. If the rapid rate of health progress in the United States since 1900 should be continued, our people may have longer lives than the people of any other nation."

A difference in reporting deaths accounts for some of the changes in rates in 1900 and in the present. The editorial says:

"Although the mortality rate from all causes combined has declined for every age group since 1900, the number of deaths per thousand population from heart diseases has increased for all age groups over thirty-five, from cancer for every age group, and from diabetes for age groups over forty-five. Some of these increases are the result of improved diagnoses of the causes of death and changes in record-keeping. Many deaths in 1900 that would have been attributed to ill-defined causes would, under present-day procedures, have been attributed to heart diseases, cancer, or diabetes."

Accident Rate High

The authors point out that although heart diseases account for more than five times as many deaths as accidents and twice as many life years lost, nevertheless fatal accidents in 1948, as in 1945 and in 1940, cut off more working lifetimes of the American people than any major cause of death. Accident prevention, the editorial says, lags far behind medical progress.

In noting the bulletin's tabulation of the changes in the major causes of death, the editorial reports:

"In this century the average age at death from each of the major causes of death has risen. The seven leading causes now account for three-fourths of our deaths, as compared with only one-half in 1900. Perhaps this fact accounts for some of the trend toward specialization in medicine. For the physician attending a patient in his final illness today is likely to be treating him for heart disease or cancer, whereas in 1900 it might have been any of a much larger number of diseases."

Praises Present System

In summarizing the importance of the progress noted in the bulletin, the AMA editorial ended with a final word of praise for American medicine: "We started the 20th century with many health disadvantages. The record of accomplishment set forth in Bulletin 92 provides the basic reason why physicians and other enlightened citizens should hold fast against any and all schemes to destroy our system of medical care under which this astounding record was made."

MINERS REPORT WELFARE FUND

The United Mine Workers Welfare and Retirement Fund, in its report for the year ending in June, 1952, lists expenditures of nearly $50 million for hospital and medical care benefits. The fund provided for 2,154 days of hospitalization and medical care for 215,372 beneficiaries throughout the bituminous coal mining communities. Miners, working or retired, and their families received 85.6 per cent of the benefits, with 4.1 per cent going to widows and orphans of deceased miners and 10.3 per cent to disabled beneficiaries who are being rehabilitated in specialized rehabilitation centers or in other institutions qualified to treat the less severely handicapped.

UMW Sponsors Hospital Associations

The same report also lists as a major development, a fund authorizing loans to the UMW-sponsored Memorial Hospital Associations of Kentucky, West Virginia and Virgina for the construction of hospitals in ten coal-mining areas. The miners' union hopes that construction of these hospitals will get under way during the coming fiscal year.

The sun is the greatest of remedies.—PLINY, Natural History, A.D. 77, quoted in *British Journal of Tuberculosis and Diseases of the Chest*, July, 1951.

✦ Reports and Announcements ✦

AMERICAN ACADEMY OF OBSTETRICS AND GYNECOLOGY

The First Annual Clinical Session of the American Academy of Obstetrics and Gynecology will be held December 15-17, 1952, at the Palmer House, Chicago, Illinois.

The meeting will feature six general sessions and forty-eight discussion groups of forty Fellows each. There also will be at least fifteen new scientific exhibits and about sixty technical displays.

The annual banquet Tuesday evening, December 16, will feature an address by the retiring president, Carl P. Huber of Indianapolis. The first truly national organization in its field, the Academy was incorporated August 14, 1951, and already has some 2400 qualified Fellows.

Election of officers will take place at the annual business meeting Tuesday morning.

Program chairman is Ralph A. Reis of Chicago.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The nineteenth annual meeting of the American College of Chest Physicians will be held at the Hotel New Yorker, New York City, May 28-31, 1953.

Physicians who wish to present papers at the meeting should submit titles and abstracts to Dr. Arthur M. Olsen, Chairman, Committee on Scientific Program, American College of Chest Physicians, Mayo Clinic, Rochester, Minnesota.

STUDENT AMA MEETING

The annual session of the House of Delegates of the Student American Medical Association will be held at the Sheraton Hotel, Chicago, December 29-30, 1952.

Dr. Walter C. Alvarez, Chicago, will speak, December 30, on "The Disappearing Art of Diagnosing with the Eyes and Ears," and Dr. John Van Nuys, dean of the Indiana University School of Medicine, will be the principal luncheon speaker the same day, discussing "A Dean and His Problems."

MEDICAL CRUISE CONGRESS

Physicians and their families are cordially invited to make application to join the Eighth International Medical Cruise Congress of the Pan American Medical Association sailing from New York on the *S. S. Nieuw Amsterdam* of the Holland-America line on January 7, 1953.

Physicians contemplating making the trip are invited to give a scientific address at one of the morning scientific sessions held each day on shipboard. The purpose of the cruise is to combine relaxation with study and to further medical contacts between members of the profession in the western hemisphere.

This twelve-day cruise will include ports in the Caribbean. The office of the Pan American Medical Association at 745 Fifth Avenue, New York 22, New York, should be contacted for further information.

PRIZE AWARD FOR PAPER ON DIABETES

The American Diabetes Association offers a $250.00 prize to *medical students* and *interns* for a paper on any subject relating to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

This incentive is particularly apropos in the field of diabetes, since Dr. Paul Langerhans made his studies of the pancreas, describing the islets that bear his name, while he was an undergraduate student in Berlin in 1869; and Dr. Charles H. Best, while a graduate student was co-discoverer of insulin in 1922.

Manuscripts must be submitted on or before April 1, 1953 to the Editorial Offices of *Diabetes:* The Journal of the American Diabetes Association, 11 West 42nd Street, New York 36, New York. The papers will be reviewed by the Editorial Board, which will take into consideration the value of the material and method of presentation in selecting the best paper.

The award of $250.00 has been made possible through the generosity of the St. Louis Diabetes Association, an affiliate of the American Diabetes Association.

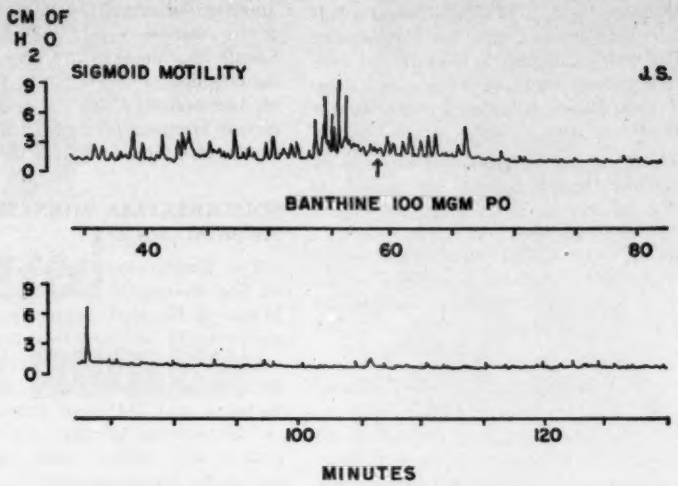
ELECTROLYTE METABOLISM SYMPOSIUM

A national symposium on electrolyte metabolism, sponsored by the M & R Laboratories, was held at the University of Minnesota, September 22-24.

Lecturers included: Dr. Daniel C. Darrow, Yale Unipersity, pediatrics professor; Dr. Willis H. Thompson, University of Minnesota, assistant pediatrics professor; and Dr. S. Danowski, University of Pittsburgh, professor of research medicine.

MINNESOTA PUBLIC HEALTH CONFERENCE

The sixth annual Minnesota Public Health Conference was held at the Saint Paul Hotel, Saint Paul, October 2-3, 1952. The meeting marked the eightieth anniversary of the creation of the Minnesota State Board of Health and was open to anyone interested in public health. At the business session, Irene Donovan, director of the Saint Paul Family Nursing Service, was elected president, replacing Dr. Charles G. Sheppard, Hutchinson; Dr. Ralph L. West, executive director of the state livestock sanitation board, first vice president; Dr. Donald R. Mackay, Saint Paul dentist, second vice president; and Allan Stone, executive director of the Minnesota division, American Cancer Society, treasurer. Dr. A. J. Chesley, executive secretary of the State Board of Health, and Dr. Harold S. Diehl, dean of the medical sciences at the University of Minnesota, were presented honorary memberships.



The effect of 100 mg. of Banthine on sigmoid motility. The contractions did not return during the experimental period.[1]

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"...has a prolonged inhibitory effect on human gastrointestinal motility....
The duration of its action is striking,...."[1]

It has also been observed that definite retardation in gastrointestinal transit time in individuals with hypermotility was attributable to the therapeutic effect of Banthine.[2]

BANTHINE® Bromide (brand of methantheline bromide)—a true anticholinergic—is available for oral and parenteral use.

1. Kern, F., Jr.; Almy, T. P., and Stolk, N. J.: Effects of Certain Antispasmodic Drugs on the Intact Human Colon, with Special Reference to Banthine (β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide), Am. J. Med. *11*:67 (July) 1951.

2. Lepore, M. J.; Golden, R., and Flood, C. A.: Oral Banthine, an Effective Depressor of Gastrointestinal Motility, Gastroenterology *17*:551 (April) 1951.

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**

CONTINUATION COURSES

A continuation course in *Gynecology for Specialists* in that field will be presented by the University of Minnesota on December 15-17, 1952. The two-and-a-half day session will be held at the Center for Continuation Study on the University campus. Subjects to be considered will include endometriosis, culdoscopy as a diagnostic tool, and gynecologic malignancy including the question of carcinoma *in situ*.

Dr. Arthur Hertig, the distinguished Professor of Pathology at Harvard Medical School, will participate in the course as a member of its faculty. The course will be presented under the direction of Dr. John L. McKelvey, professor and head of the Department of Obstetrics and Gynecology, and the remainder of the faculty will include clinical and full-time members of the staff of the University of Minnesota Medical School.

A continuation course in *Anesthesiology for General Physicians* will be presented by the University of Minnesota on January 8-10, 1953, at the Center for Continuation Study. Emphasis will be placed throughout the course on anesthesiological techniques available to practicing physicians and surgeons. Regional anesthesia will be dealt with in detail, and the management of shock will also be discussed thoroughly. A special feature will be a detailed consideration of the function and operation of a Recovery Room.

Three distinguished visitors will participate as members of the faculty for this course: Dr. Donald E. Hale, Director, Department of Anesthesiology, Cleveland Clinic, Cleveland, Ohio; Dr. Sidney O. Orth, Professor and Director, Department of Anesthesiology, and Professor of Pharmacology, University of Wisconsin Medical School, Madison, Wisconsin; and Dr. Daniel C. Moore, Chief of the Anesthesiology Section, Virginia Mason Hospital, Seattle, Washington. The course will be presented under the direction of Dr. Ralph T. Knight, Director, Division of Anesthesiology, and the remainder of the faculty will include members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

SOUTHWESTERN MINNESOTA MEDICAL SOCIETY

The Southwestern Minnesota Medical Society held its first meeting in a series of four at the Worthington Municipal Hospital, September 15. The dinner meeting was attended by thirty-two doctors and their wives.

Dr. A. B. Rosenfield, director of the Division of Maternal and Child Health for the State Health Department, and Dr. Alex Barno, of Minneapolis, spoke on the maternal mortality rate in Minnesota. In comparison with studies from other states, Minnesota has one of the lowest maternal death rates.

HEALTH DEPARTMENT LAUNCHES NEW PROGRAM

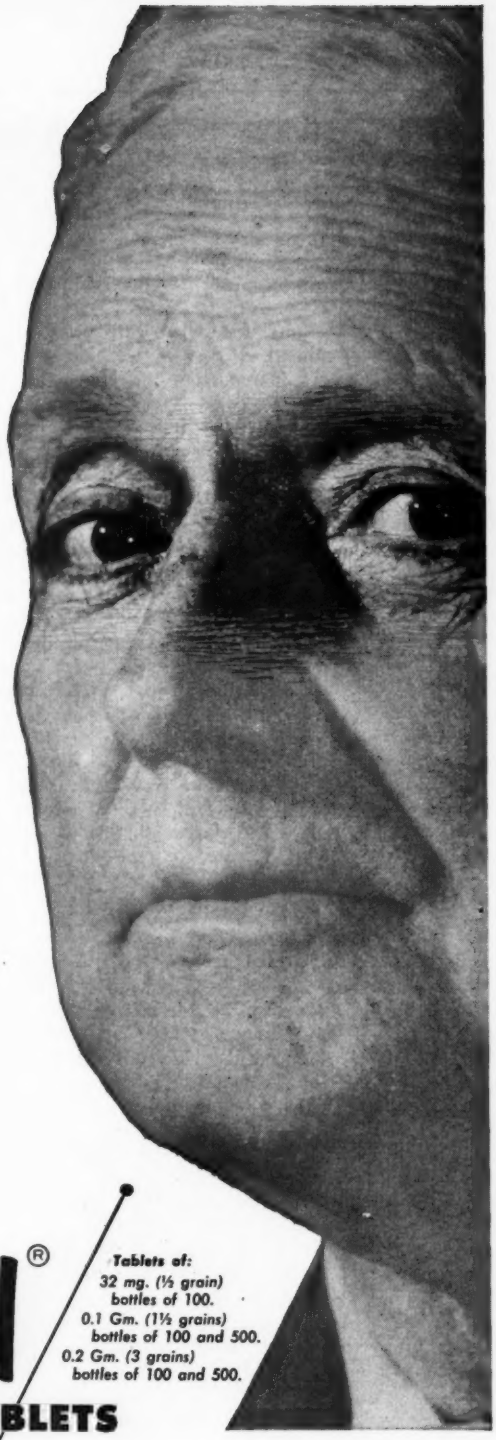
The Minnesota Department of Health is launching a new type of program in professional education for physicians this fall and winter. Pathological conferences on cancer and heart disease are being scheduled as a part of regular hospital staff meetings.

During the past three years the Department of Health has sponsored seminars on heart disease and cancer throughout the state. Each consisted of a two-hour session for eight consecutive weeks. Three professional groups, physicians, dentists and nurses attended these seminars. Essentially, the method of teaching in the seminar was by means of the formal lecture with time following for questions. The conference, on the other hand, is a more informal program with greater freedom of "give and take" between the guest consultant and the audience. Hospital staffs, being smaller than seminar groups, make for closer feeling and more opportunity on the part of those attending to participate in the discussion.

The conference is led by a guest consultant who reviews with the group well worked up case histories of typical cancer and heart patients. The prime purpose in these meetings is to exchange information on diagnosis and treatment of these common every-day cases with these diseases. By means of problem presentation and questioning much information can be exchanged among those attending. Informality and free participation governs the entire sessions. Slides, x-ray film, and mimeographed material are used to supplement the presentation by the guest consultant.

The conferences are sponsored by the Minnesota Medical Association, University of Minnesota School of Medicine, Minnesota Cancer Society, Minnesota Heart Association as well as the Minnesota Department of Health.

Relaxed but awake



In emotional and nervous disorders, Mebaral exerts its calming influence without excessive hypnotic action.

Mebaral is also a reliable anticonvulsant.

INDICATIONS:

Because of its high degree of sedative effectiveness, Mebaral finds a great field of usefulness in the regulation of agitated, depressed or anxiety states, as well as in convulsive disturbances. Specific disorders in which the calming influence of Mebaral is indicated include neuroses, mild psychoses, nervous symptoms of the menopause, hypertension, hyperthyroidism and epilepsy.

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Tasteless **TABLETS**

Tablets of:
32 mg. (½ grain) bottles of 100.
0.1 Gm. (1½ grains) bottles of 100 and 500.
0.2 Gm. (3 grains) bottles of 100 and 500.

WINTHROP-STEARNS INC. New York 18, N.Y., Windsor, Ont.

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In Memoriam

JOHN A. BROBERG

Dr. John A. Broberg, a practitioner at Blue Earth, Minnesota, for many years, died October 13, 1952, at the age of ninety.

Dr. Broberg was born in Sweden, July 5, 1862, and came to this country at the age of five. He and his future wife both graduated from the University of Valparaiso, Indiana, in 1888 and they were married August 20, 1889. His medical degree was obtained from the University of Michigan medical school in 1892.

Dr. Broberg practiced at Delevan for six years before settling in Blue Earth in 1898. He retired from practice in 1942, after rounding out fifty years of service to his community. On August 20, 1949, Dr. and Mrs. Broberg celebrated their sixtieth wedding anniversary. Mrs. Broberg is still living at the age of ninety. Two daughters, three grandsons and four great-grandchildren also survive him.

Dr. Broberg was a charter member of the Blue Earth Valley Medical Society and was elected its first secretary. The pioneer physician was city health officer from 1902 until 1947.

Dr. and Mrs. Broberg liked to travel to far-away places. On one occasion they viewed the midnight sun from Fort Yukon in Alaska and a few years later from Hammerfest, Norway.

JAMES HOUGHTON DRAKE

Dr. James H. Drake, for many years a resident of Baudette, Minnesota, died at La Mesa, California, October 11, 1952.

Dr. Drake was born March 14, 1878, in Chicago. He graduated from Hahnemann Medical College in Chicago in 1903, attended the University of Minnesota and interned at Minneapolis City Hospital.

He practiced medicine in Alexandria, Minnesota, Hardin, Montana, and Hibbing before going to Baudette in 1919 as physician for the International Lumber Company. His war service included Spanish-American war duty as a private in the First Illinois Volunteer Infantry in 1898. He saw action at San Juan Hill, Cuba. During World War I he served as a captain in the medical corps. He was active in the Veterans of Foreign Wars from the time of its organization and was a leader of Peter Graham Post 2948 for many years. He was also active in the Elks Lodge and the Masonic Order.

Dr. Drake married Clarabel Moses of Alexandria, Minnesota, in 1907. His wife and a daughter, Jean, survive him.

EDWARD WILBROD FAHEY

Dr. Edward W. Fahey, Saint Paul, passed away at St. Joseph's Hospital on October 5, 1952. He was seventy-six years of age.

Dr. Fahey was born November 18, 1876, in Kingston, Ontario. He graduated from Queens Medical College at Kingston, Ontario, in 1901 and interned for twenty months at St. Mary's Hospital in Rochester, New York, before settling in Duluth in 1904. He practiced in Duluth until 1924 when he became the supreme physician for the Knights of Columbus and moved to Saint Paul. He retired in 1948.

In 1939, Dr. Fahey was made Knight Commander of the Order of St. Gregory by Pope Pius XI for his outstanding service as a layman.

Dr. Fahey was a member of the Ramsey County Medical Society, the Mimesota State Medical Association and American Medical Association. He is survived by two sons, Edward J. and John W., and a daughter, Margaret, all of Saint Paul.

SIM B. LOVELADY

Dr. Sim B. Lovelady, a member of the Mayo Clinic staff in the section of obstetrics and gynecology from 1940 to 1949, died of a heart attack October 8, 1952, at Houston, Texas. He left the Clinic in August, 1949, to enter private practice at Houston.

Dr. Lovelady was born January 11, 1909, at Danville, Alabama. He received his M.D. degree in 1934 from Tulane University, New Orleans. He was an intern at Charity Hospital, New Orleans, in 1934 and 1935. In 1935, he came to Rochester as a fellow in surgery in the Mayo Foundation and in 1939 became a first assistant in clinical obstetrics and gynecology.

Dr. Lovelady entered the medical corps of the army in August, 1942, as a major and was promoted to the grade of lieutenant colonel. He was assigned successively to the Army Medical Center in Washington, D. C., the 182nd General Hospital in New Orleans and served with the latter component in England and Ireland.

Dr. Lovelady was a fellow of the Royal Society of Medicine of England, the Central Association of Obstetricians and Gyencologists, the Minnesota Society of Obstetrics and Gynecology, Sigma Nu academic fraternity and Phi Chi medical fraternity.

Dr. Lovelady is survived by his wife, the former Mary Greer, three sons and a daughter.

OSWALD LEICHT

Dr. Oswald Leicht, for years a resident of Winona, Minnesota, died October 16, 1952, at a Sheboygan, Wisconsin, hospital following an illness of two years. He was born in Fountain City, Wisconsin, April 29, 1875. He received his M.D. degree from Northwestern University in 1898 and after practicing a short time went to London and Vienna to take spe-

(Continued on Page 1068)

OSWALD LEICHT

(Continued from Page 1066)

cial studies in eye, ear, nose and throat diseases. He returned to Winona in 1900.

Dr. Leicht was active in musical and civic activities, having been the organizer of the Winona Symphony Orchestra in 1908 and the Winona Municipal Band in 1916. He was a past president of the Winona Board of Municipal Works and a past member of the Minnesota State Board of Medical Examiners. He was one of the oldest active members of the Winona Kiwanis Club.

He became president of the Winona Machine and Foundry Company in 1910 but continued the practice of medicine until the beginning of World War II. He then took over the active management of the foundry with his three sons.

In 1901, Dr. Leicht married Margaret Gardner. She died in 1928. His son, Joseph, died in 1949 as a result of injuries received when struck by a car. Two sons, Robert of Ramey, Puerto Rico, and Edward, of Sheboygan, survive him.

Nations like Sweden and the United States of America, which have been able to make the relatively small investment involved in a sound public-health program, have reaped a rich harvest in life capital as a result.—C. E. A. WINSLOW, The Cost of Sickness and the Price of Health, WHO Monograph Series, No. 7, 1951.

Of General Interest

Dr. Robert N. Barr, deputy executive officer of the Minnesota Department of Health, spoke on the status of public health in Minnesota, at the annual meeting of the Koochiching County Public Health Nursing Advisory Committee, held September 22, at International Falls.

* * *

Three new doctors in the area—**Drs. Milton Kaiser,** New Ulm, **Rueben Rayner** and **Harley Raser,** Gibbon, joined the Brown-Redwood-Watonwan County Medical Society, September 18, at the regular meeting.

* * *

Presenting papers at the American College of Surgeons meeting held in New York September 22-27 were **Drs. Yoshio Sako** and **Richard L. Varco** of the University of Minnesota and seventeen members of the Mayo Clinic staff. The Mayo Clinic members were **Drs. G. S. Baker, E. A. Banner, W. H. Bicker, H. W. Dodge, F. A. Figi, J. H Grindlay, G. A. Hallenbeck, S. W. Harrington, F. Z. Havens, E. D. Henderson, J. M. Janes, E. S. Judd, J. W. Kirklin, K. A. Lofgren, J. T. Priestley, Grace Roth** and **G. J. Thompson.**

Dr. Priestley is a member of the Board of Governors of the College and of the Committee on Graduate Training in Surgery.

* * *

Dr. Arthur H. Wells, pathologist, St. Luke's Hospital, Duluth, spoke on advances in cancer research, at a meeting of the American Cancer Society, Duluth District, September 10. Dr. Wells recently attended the Second National Cancer Conference in Cincinnati, Ohio.

* * *

Dr. D. R. Hastings, director of Glen Lake Sanatorium out-patient department, spoke to the members of the board of directors of the Hennepin County Tuberculosis Association on September 19 on nutrition needs of persons who have or have had tuberculosis.

* * *

Dr. Alfred Uihlein, Mayo Clinic neurologic surgeon, was elected to the Board of Trustees of Shattuck Military School, Faribault, in September.

* * *

Dr. J. S. Lundy, Rochester, has been appointed a member of the Mineral Springs Sanatorium Commission. He replaces John T. Lemmon in September.

* * *

Dr. Fred G. Carter, former superintendent of Ancker Hospital, Saint Paul, now administrator of St. Luke's Hospital in Cleveland, was given an award of merit for his "leadership and vision . . ." by the American Hospital Association, September 18. Dr. Carter was superintendent of Ancker Hospital from 1924 to 1935 and assistant superintendent for four years prior to 1924.

* * *

Dr. Robert N. Barr and **Helen L. Knudsen** of the State Board of Health, conducted a meeting at Cloquet, October 6, to present the hospital needs of the area to the people of Carlton County.

* * *

Lake County will be the first Minnesota county to sponsor an x-ray survey for the second time. Dr. John A. Jumer, county chairman of the survey, said that the actual x-raying will begin November 17.

* * *

Drs. William R. Blomberg and **Theron W. Nelson** of Princeton; **Drs. Ernest S. Hagquist** and **Clarence J. Henry,** Milaca, were ordered to report for preinduction physical examinations, September 26.

* * *

Eleven Twin City physicians became fellows in the American College of Surgeons, September 26. They were: **Drs. Samuel Beirstein, Lyman B. Clay, Edgar G. Ingalls, Jr., Arnold J. Kremen, Floyd J. Lewis, Virgil J. P. Lundquist, Malvin J. Nydahl, Lloyd F. Sherman, Joseph P. Spano, John P. Wendland,** and **Richard L. Varco.**

* * *

Dr. Robert B. Howard, instructor, and **Dr. Carleton Chapman,** associate professor, School of Medicine, University of Minnesota, spoke at the annual Farm Bureau Women's Short Course held at the University Farm in Saint Paul, September 9 to 12. Dr. Howard spoke on problems of the aged and Dr. Chapman on diet and disease.

* * *

Dr. H. L. Smith, Mayo Clinic staff, addressed the St. Louis Academy of General Practice at St. Louis, Missouri, September 23, on "The Movements and Sounds of Heart Valves."

* * *

Dr. Andrew A. Gage, Buffalo, New York, joined the recently incorporated Hartfiel Medical Center, in September. Dr. Gage is a 1944 graduate of the University of Buffalo School of Medicine and specialized in surgery at Meyer Memorial Hospital, Buffalo, and Veterans Administration Hospital, Batavia, New York. Dr. Gage will be located in Montevideo but will spend part of each week in Maynard.

* * *

Dr. John H. Grindlay, of the Mayo Clinic staff, is one of the three representatives of the American Medical Association named to a joint commission to undertake a study of surgical materials; data of the study to be made available to all surgeons. Others on the AMA team are Dr. Ralph E. DeForest of Chicago and Dr. I. Mims Gage of New Orleans.

The joint commission is made up of the American Academy of Orthopedic Surgeons, American College of Surgeons, American Surgical Trade Association and the AMA.

* * *

Drs. Seigfried Oeljen and **R. D. Davis** of Waseca, received orders to report for their physical examinations, September 30, prior to possible induction into the Armed Forces.

* * *

Dr. E. J. Engberg, superintendent of the Minnesota State School and Colony, Faribault, was re-elected president of the Rice County Public Health Association at the annual meeting, September 25.

Attending the twenty-eighth annual meeting of the Alumni Association of the Mayo Foundation, September 26-27, were **Drs. Walter G. Benjamin,** Pipestone; **H. A. N. Mattson, O. H. Wangensteen, R. M. Wilder, Jr., J. M. Hayes, Thomas J. Kinsella, L. M. Larson** and **Clyde M. Cabot** of Minneapolis; **E. E. Christensen,** Winona; **W. P. Freligh,** Albert Lea; **P. W. Harrison,** Worthington; **R. W. Kearney,** Mankato; and **T. O. Young,** Duluth.

* * *

Winners of Minnesota Medical Foundation scholarships were Duane Flagstad, St. James; and Maynard E. Jacobson, South Saint Paul. They and eleven other University of Minnesota medical students each re-

ceived a $500 check, October 2, from **Dr. Owen Wangensteen,** president of the Foundation and head of the University's department of Surgery.

* * *

The documentary short film, "Your Doctor," has received the indorsement of the doctors in Wabasha County. **Dr. Doreen Martin,** president of the Wabasha County Medical Society, said that the film shows the problems of practicing in rural communities and the relationship of a practicing physician to his professional organizations.

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Dr. A. B. Hagedorn, Mayo Clinic, spoke on the anemias to the members of the Southwestern Minnesota Medical Society and auxiliary at the regular meeting of the Society at Worthington, September 29.

* * *

Drs. Thomas J. Sisterman and **Edward P. Donatelle** opened a new medical clinic at Fifty-fourth Street and Penn Avenue South, Minneapolis, in September.

* * *

A testimonial banquet for **Dr. Harry N. Sutherland** of Shipman Hospital staff and health officer for the Ely community, was held in Ely September 30. The event was planned jointly with the Tuberculosis and Health Association of St. Louis County. Besides having presided at the births of about 3,000 of Ely's population, Dr. Sutherland was in charge of the first mobile x-ray survey conducted in the world.

* * *

Dr. George F. Lull, secretary and general manager of the AMA, was married to **Miss Mildred Louise Backman** on September 10, at Fremont, Nebraska. Miss Backman has served in a secretarial capacity for the AMA Council in Medical Service for several years. Dr. and Mrs. Lull have gone to Athens, Greece, where Dr. Lull will attend the annual meeting of The World Health Association.

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An anesthetic machine was presented to the Luverne Hospital board, Luverne, September 17, as a memorial to **Dr. O. W. Anderson** who died this spring.

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Dr. S. T. Kucera, Northfield Hospital staff, spoke at the annual silver tea of the Northfield City Hospital Auxiliary, September 19. Dr. Kucera accented the crowded conditions and stressed the need of enlarging present facilities.

* * *

Dr. Thomas Lowry, chief of staff at Minneapolis General Hospital, outlined the hospital's functions, organization, facilities and staff to the hospital committee, September 26. The hospital committee was organized by the Citizens League of Greater Minneapolis to study the city and county needs for a new general hospital.

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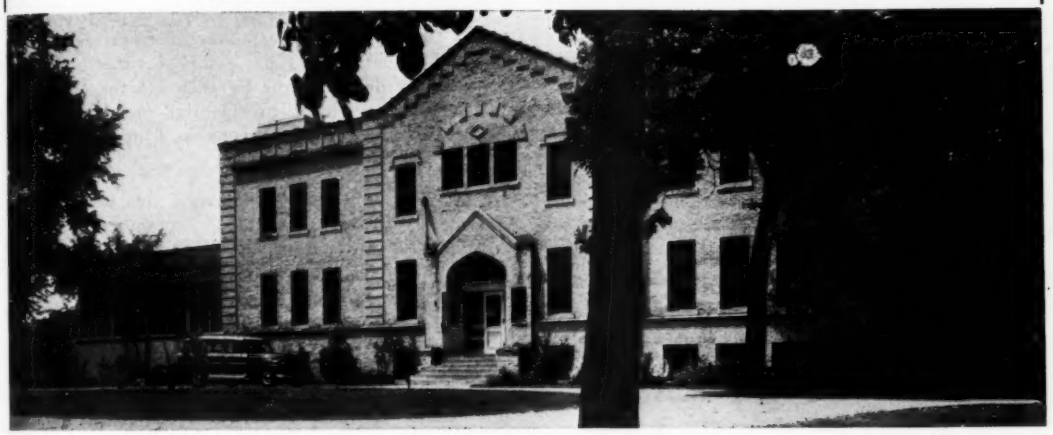
Concluding more than forty-eight years of service to the community, **Dr. J. W. Preisinger,** Renville,



was honored at a retirement dinner, September 15. **Dr. Robert B. Pierce,** on behalf of the Renville Civic and Commerce Association, presented Dr. Preisinger with a pen and pencil set.

* * *

Dr. Donald P. Chance, on the surgical staff of the Mayo Clinic, was married Septmember 10 to Marie Elizabeth Gartley, member of the anesthesia staff at the Mayo Clinic.

* * *

Dr. Frederic J. Kottke, director of the division of physical medicine at the University of Minnesota, spoke on aid to the handicapped at the second annual meeting of the Duluth Rehabilitation Center, Inc.

* * *

The Sheard-Sanford Photelometer Royalty Award for 1952 was presented to **Dr. Frank D. Mann,** Mayo Clinic staff, department of clinical pathology, at the meeting of the American Society of Clinical Pathologists held in Chicago, October 12-17. The award of $500 is given "in recognition of meritorious research work by a member of the society under the age of forty years."

* * *

Dedication of **Frank C. Mann Hall** in the new Medical Sciences building, Rochester, September 26, honored a career of thirty-eight years of medical research. **Dr. Mann** retired from the Mayo Clinic and Mayo Foundation on October 1.

Dr. Mann came to Rochester in 1914 to serve as director of experimental medicine at the Mayo Clinic and to take charge of the pathologic anatomy service that had been established by the late Dr. Louis B. Wilson in 1905. When the Mayo Foundation was created in 1915 as a part of the Graduate School of the University of Minnesota, Dr. Mann became assistant professor of experimental surgery and pathology. He became a full professor in 1921.

In 1932, Dr. Mann was awarded the William Wood Gerhard gold medal of the Philadelphia Pathological society, and in 1937 Georgetown University conferred an honorary degree of doctor of science on him. A year later Indiana University honored him with the degree of doctor of laws. In 1950, he became one of the only two members of the staff of the Mayo Clinic and Mayo Foundation to be elected to membership in the National Academy of Sciences. The other Rochester man similarly honored was **Dr. E. C. Kendall.**

* * *

Dr. M. M. Williams, assistant superintendent and medical director of Ah-Gwah-Ching, the Minnesota State Sanatorium near Walker, was named president of the institution by F. W. Nichols, state director of social welfare, October 1. Dr. Williams continues as medical director under the new appointment.

Dr. Williams joined the sanatorium as a staff physician in 1936, remaining there until 1943, when he left to serve in the army for four years. During

this period he spent two years as a chest disease specialist at Fitzsimons General Hospital, Denver, Colorado.

* * *

To be married, December 20, are Marilyn Clark, Duluth, and **Dr. Roger Stanley Johnson,** Deephaven. Dr. Johnson was graduated from the University of Minnesota Medical School and interned at Ancker Hospital, Saint Paul. Miss Clark is a graduate of the University of Minnesota School of Nursing and the School of Public Health.

* * *

Dr. Donald C. Balfour, director emeritus of the Mayo Foundation and professor of surgery in the Foundation, delivered the Seventh Martin Memorial lecture at the recent presidential meeting of the American College of Surgeons in Chicago.

* * *

Four doctors from the Plainview area who reported for physical examinations, September 30, prior to induction into the armed forces, were **Drs. D. G. Mahle,** Plainview; **E. W. Ellis,** Elgin; **C. G. Ochsner** and **B. J. Bouquet,** Wabasha.

* * *

Dr. William R. Jones spoke on "The Vote" when giving the outgoing president's address to the Hennepin County Medical Society, October 6. **Dr. Claude J. Ehrenberg** became the new president and Dr. Jones, chairman of the board.

* * *

Dr. J. Gordon Beaton joined **Drs. S. T. Kucera** and **G. N. Rysgaard** in their offices in the Medical Arts Building, Northfield, in September. Dr. Beaton was graduated from the University of Minnesota School of Medicine and had his internship in Baltimore. During World War II, he served with the United States Public Health Service; after the war he did graduate work in internal medicine. Before coming to Northfield, Dr. Beaton practiced for a year and a half at New Ulm.

* * *

Dr. W. F. Wilson, Lake City, was elected secretary and treasurer of the Wabasha County Medical Society for the fifty-seventh time at the annual meeting held at Plainview in October. Dr. Wilson was first elected to the position of secretary-treasurer in 1896 and has been re-elected annually ever since. **Dr. E. C. Bayley,** Lake City, was elected president; **Dr. C. G. Ochsner,** Wabasha, vice president; **Dr. B. A. Flesche,** Lake City, assistant secretary. Dr. Bayley was also named delegate to the state convention.

Speakers at the meeting included **Dr. Dorene Martin,** Pepin, formerly of Wabasha; **Drs. D. J. Erickson, Haddon M. Carryer, J. A. Bargen** and **R. L. Kennedy** of the Mayo Clinic; and **Drs. Percy T. Watson** and **John T. Smiley** of the State Board of Health.

HOSPITAL NEWS

The new **Hudson Memorial Hospital,** a fireproof building, to cost $430,000 is tentatively set to open in late November. It is located in a wooded plateau on Liberty Hill overlooking the St. Croix river and will have a capacity of thirty-two beds.

The hospital has received no government aid. Steps were taken in providing a hospital for Hudson with the establishment of the William H. Phipps Foundation by Mr. and Mrs. Stephen C. Phipps in 1946. To this sum was added a substantial gift by Mr. and Mrs. Charles A. Ward and $40,000, as well as the hospital site, by the city of Hudson.

Architects for the two-story red brick building are Ellerbe and Company of Saint Paul. The general contractor is the Olson Construction Company of Stillwater. All rooms are equipped with large picture windows and central oxygen supply is piped to each room. Static electricity is eliminated by special floor surfacing.

The new hospital will supply first-class hospital accommodations for the city of Hudson and the St. Croix valley from Stillwater to Afton.

* * *

Dedication services for the multi-million dollar enlargement of the **Medical Sciences** building of the **Mayo Clinic** and the **Mayo Foundation for Medical Education and Research** were held September 26 and 27, 1952, at Rochester.

Bronze statues of the Doctors Mayo were unveiled by Dr. C. W. Mayo, son of Dr. Charles Mayo and Mrs. D. C. Balfour, daughter of Dr. Will Mayo. The statues of the two brothers stand beside that of their father, Dr. William Worrall Mayo.

Dr. Vannevar Bush, president of the Carnegie Institution of Washington, spoke at the opening ceremony. Speakers during the dedication included Dr. Owen Wangensteen, former Mayo fellow and chief of surgery at the University of Minnesota, who talked on the impact of physiology on surgery; Dr. Lester R. Dragstedt, chairman of surgery, University of Chicago, spoke on contributions of experimental medicine to knowledge of peptic ulcers; and Dr. Chester M. Jones, clinical professor of medicine, Harvard University, and physician at Massachusetts General Hospital, Boston, spoke on the role of experimental medicine in understanding the function of the liver.

One part of the new building, now remodeled, was put up in 1941. The five-story addition with two underground levels more than triples the floor space. Most of the buildings' space is devoted to research and medical education facilities.

* * *

Dedication services for the new **St. Francis Hospital** at Breckenridge were held September 17, 1952. Dr. Roger Kennedy, president of the Minnesota State Medical Association, participated in the ceremonies along with Gov. C. Elmer Anderson, Gov. Norman

Brunsdale of North Dakota, and Bishops Peter W. Bartholome of St. Cloud and Leo Dworschak of Fargo.

* * *

A new twenty-four bed **psychiatric center for children** at the University of Minnesota is expected to open this month. The new unit will not only provide better patient care but also a better opportunity for research, and training physicians and nurses. It will include facilities for recreational and occupational therapy.

The center was set up with a $115,000 grant from the 1951 Legislature. Dr. Irvine McQuarrie, head of the pediatrics department, said only a few states have comparable facilities. The center will be the first in the state for exclusive hospitalization of mentally ill children.

Dr. Reynold Jensen, professor of pediatrics, will be the medical director of the unit. His staff will include Dr. Jack Wallinga, psychiatrist; Wendell Quast, senior clinical psychologist, and Elsworth Stenswick, speech clinician.

* * *

Minnesota has one of the lowest rates of draftee rejection for reasons of physical, mental and moral unfitness for military service—20 per cent. Our state shares this distinction with Kansas and North Dakota. In comparison, South Carolina boys were turned down at a rate of 63 per cent, 56 per cent in Arkansas and over 50 per cent in Alabama, Georgia and Mississippi.—Christmas Seal Health News Service.

BLUE CROSS-BLUE SHIELD NEWS

Blue Shield

With revised Blue Shield contract and Schedule of Payments in effect and distributed to both physicians and subscribers on the first of October, a more active professional and public relations program is being geared for immediate action. In fact, such a plan includes talks and question and answer sessions at staff and medical meetings, a revitalized correspondence department, and the compilation and preparation of a physician's manual for later distribution. While this plan is at present in its initial and formative stages, there is already evidence of general acceptability and success.

During the program's first two weeks, three invitations were received to discuss the new benefits and contract at hospital staff, medical and group leader meetings. These assignments are covered by the medical director and either Mr. Ben Stephens, Jr., who is serving as Acting Manager of the Claims Department, or Mr. Robert Kermott, who is organizing the Professional and Public Relation section of Blue Shield. In talks already given and for those at present scheduled, formal remarks of the speaker are very brief following which those in attendance are encouraged to ask questions regarding any or all features of the Blue Shield program.

Through the past several months two meetings of receptionists, secretaries and office nurses have been held to clarify all matters of filing claims. In addition to the meetings with physicians as discussed, an effort

is to be made to meet with the persons in the doctors' offices and to organize such meetings in rural districts about the state. However, further steps in this phase of the work can be taken only with additional help as the program develops.

Another feature of the present plan is the tentative reorganization of the correspondence and telephone inquiry section. All in-coming mail is being classified and routed to persons who are best trained and qualified to answer it. Mail is being answered much more rapidly with emphasis placed upon promptness and complete explanation of all contract features involved. This policy, in effect for several months, applies to all letters, those of subscribers as well as physicians. The effectiveness is apparent in that there are fewer letters of inquiry and complaint from both doctors and subscribers, and there has been some increase in the number of "thank you" and appreciation letters.

Work on a physician's and procedure manual was started several months ago. One of the first moves in this direction was the assembling of such manuals from as many other Blue Shield plans as possible. This having been done, selection, organization and preparation of material most needed and used by doctors and their office personnel has been and is under way. Final completion of this project is not in prospect for some time insofar as the material presented by such a manual will depend upon findings from a review of other such manuals, nature and volume of complaints and inquiries now and in the past received, and the impressions gained from the more active and energetic professional and public relations program.

This entire project is being developed as a co-operative and educational program for both subscribers and doctors. Its helpfulness and success will depend upon the requests and suggestions regarding it received from the practicing physicians of the state.

Blue Cross

Blue Cross has been in existence nationally since 1933, Minnesota being one of the pioneer Plans, and it was not until January 1, 1937 that enrollment nationally passed the half-million mark.

In the fifteen-year period between January 1, 1937 and January 1, 1952 the population of this country increased about 19 per cent. General hospital admissions increased, however, no less than 104 per cent, but Blue Cross membership during these fifteen years increased sixty-three times to hit the total of 38,515,000. On July 1 of this year, national Blue Cross enrollment stood at 39,462,000. That is an increase of more than sixty-four times over what it was on January 1, 1937.

Let us take a shorter perspective. Hospital admissions in the United States increased from 15,829,000 in 1947 to 18,237,000 in 1951. That is a net increase of 2,408,000 annual admissions. During these same years, Blue Cross membership in the United States increased from 27,532,000 to 38,515,000, an increase of 10,983,000 participant subscribers. For the whole span of the fifteen-year period we have considered, Blue Cross enrollment in-

creased at the rate of more than 2,500,000 new participants per year.

Fifteen years ago Blue Cross covered a fraction of 1 per cent of the American people. Today it covers 25.7 per cent of the people. If management in the Steel industry, the automobile industry, and many other industries covered by Blue Cross did not think Blue Cross the most adequate and effective method of financing hospital services; if the Farm Bureau and the Grange, the many trade associations, and the million of individuals covered by Blue Cross did not think so, could Blue Cross have grown so consistently from year to year? Could it have achieved the phenomenal manifestation of public acceptance that it has?

In 1951 Blue Cross payments to all hospitals in the United States amounted to $443,902,000. That was 26.1 per cent of hospital income. The important fact then is that while Blue Cross covered 24.9 per cent of the people, it paid 26.1 per cent of the national hospital bill. This information is furnished you in view of the interest that the Federal government appears to have in the problem of financing health services to the people. The Federal government, the nation's largest employer, the one most vocal on this problem, has yet failed to make any provision for helping its own employes and their dependents to get any kind of financing of their health needs. The Federal government has failed so far to take so rudimentary a step as the allowing of payroll deductions in order to facilitate medical-hospital group coverage for its employes.

Increasing numbers of the nation's large employers are recognizing the desirability of making a contribution to the financing of health services for their employes. Why is the Federal government so far behind private industry? Is there a wish on the part of some not to be too successful in solving by voluntary means an acute social problem that has often provided useful political ammunition?

The phenomenal public acceptance Blue Cross and Blue Shield have won in so short a time from every segment of the population shows that the people find Blue Cross and Blue Shield the most adequate and most effective method of financing hospital and medical services. Blue Cross and Blue Shield have developed a national program which uses its local strength to meet national needs. Through their many devices for enrolling every type of group, Blue Cross and Blue Shield have revealed their intention and their ability to develop into a universal system of hospital and medical service serving the whole community.

Financial

During the first eight months of 1952, $2,478,592 has been paid out by the Blue Shield Plan to doctors of medicine for services rendered to Blue Shield subscribers, and Blue Cross has paid out $8,269,971 to hospitals for services rendered to Blue Cross subscribers.

BOOK REVIEWS

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical Libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

BOOKS RECEIVED FOR REVIEW

SYNOPSIS OF OBSTETRICS. Fourth Edition. J. C. Litzenberg, B.Sc., M.D., F.A.C.S. Late Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis; revised by Charles E. McLennan, M.D., Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco. 368 pages. Illus. Price $5.50, flexible binding. St. Louis: C. V. Mosby Co., 1952.

SYNOPSIS OF PATHOLOGY. Third Edition. W. A. D. Anderson, M.A., M.D., F.A.C.P. Professor of Pathology, Marquette University School of Medicine, Pathologist, St. Joseph's Hospital, Milwaukee, Wisconsin. 788 pages. Illus. Price $8.00, flexible binding. St. Louis: C. V. Mosby Co., 1952.

THE HISTORY OF AMERICAN EPIDEMIOLOGY. C. E. Winslow, Dr. P.H., Professor Emeritus, Yale University School of Medicine, editor, American Journal of Public Health; Wilson G. Smillie, M.D., Professor and Chairman, Department of Public Health and Preventive Medicine, Cornell University Medical College; James A. Doull, M.D., Medical Director, Leonard Wood Memorial (American Leprosy Foundation); John E. Gordon, M.D., Professor and Chairman, Department of Epidemiology, School of Public Health, Harvard University. Edited by Franklin H. Top, M.D., Professor of Epidemiology and Pediatrics, College of Medical Sciences, University of Minnesota. 190 pages. Illus. Price $4.75, cloth. St. Louis: C. V. Mosby Co., 1952.

LOW FAT DIET COOK BOOK. Dorothy Myers Hildreth and Eugene A. Hildreth, M.D. Introduction by Francis C. Wood, M.D. 135 pages. Price $2.95, cloth. New York: Medical Research Press, 1952.

CORRELATIVE NEUROANATOMY AND FUNCTIONAL NEUROLOGY. Sixth Edition. Joseph J. McDonald, M.S., M.Sc.D., M.D., Professor of Surgery, Columbia University; Attending Surgeon, Presbyterian Hospital, New York; Director of the Surgcial Service, Francis Delafield Hospital, New York; and Joseph G. Chusid, A.B., M.D., Attending Neurologist, St. Vincent's Hospital, New York. 263 pages. Illus. Price $4.00, flexible binding, paper cover. Los Altos, California: Lange Medical Publications, 1952.

PROGRESS IN FUNDAMENTAL MEDICINE. Paul Cannon, M.D., University of Chicago; J. A. Cunningham, M.D., University of Alabama; Paul Klemperer, M.D., Mount Sinai Hospital, New York; Albert Kligman, M.D., University of Pennsylvania; G. K. Mallory, Mallory Institute; Tracy B. Mallory, M.D. (deceased), Massachusettes General Hospital; J. C. Paterson, M.D., University of Western Ontario; L. B. Stoddard, M.D., University of Kansas; W. Kenneth Cuyler ,M.D., Duke University; J. P. Wyatt, M.D., St. Louis University. Edited by J. F. A. McManus, M.D., University of Virginia. 316 pages. Illus. Price $9.00, cloth. Philadelphia: Lea & Febiger, 1952.

A 40-YEAR CAMPAIGN AGAINST TUBERCULOSIS. Louis J. Dublin, Ph.D., Second Vice President and Statistician, Metropolitan Life Insurance Company. 115 pages. Illus. Cloth binding. New York: Metropolitan Life Insurance Co., 1952.

REVIEW OF PHYSIOLOGICAL CHEMISTRY. By Harold A. Harper, Ph.D., Professor of Biology (Biochemistry), University of San Francisco; Lecturer in Surgery, University of California School of Medicine, San Francisco; Biochemist Consultant to Metabolic Research Facility, U. S. Naval Hospital, Oakland; Director, Biochemistry Laboratory, St. Mary's Hospital, San Francisco. 3d ed. 260 pages. Spiral binding. Paper. Price, $3.50. Palo Alto, Calif.: University Medical Publishers, 1951.

In outline form, well indexed and with significant terms underlined, this represents the answer to the crammer's prayer. Its orderly context clear and moderately limited detail will appeal to the student, also. It is an excellent review for state and specialty board examinations.

WILLIAM J. HULTGEN, M.D.

ADVANCES IN PEDIATRICS. Editor, S. Z. Levine, Cornell University Medical College; Associate Editors: Allan M. Butler, Harvard Medical School; Margaret Dann, Cornell University Medical College; L. Emmett Holt, Jr., New York University College of Medicine; A. Ashley Weech, University of Cincinnati College of Medicine. Vol. 5. 273 pages. Illus. Cost $7.00. Chicago: Year Book Publishers, 1952.

This volume, like its predecessors, provides a worthy contribution to current pediatric knowledge. It consists of six articles on subjects of active interest. Three are by American contributors and three, which are on Vitamin K in relation to hemorrhagic disease of the newborn, BCG vaccination, and angiocardiographic studies, are from Denmark and Sweden. The subjects are written by those actively engaged in the field and are comprehensively covered. Particularly is this true of the article on the nephrotic syndrome in children. The remaining topics discussed are treatment of the bacterial meningitides and iron metabolism.

Pediatricians in particular will be grateful to the editors and contributors for this fine presentation of material enabling them to keep abreast of the latest information in these important fields.

GERALD I. FREEMAN, M.D.

RYPINS' MEDICAL LICENSURE EXAMINATIONS; TOPICAL SUMMARIES AND QUESTIONS. By Walter L. Bierring, M.D., F.A.C.P., M.R.C.P., Edin. (Hon.) with the collaboration of a review panel. 7th ed. 856 pages. Price $8.00. Philadelphia: Lippincott, 1952.

Covering the subjects of anatomy, physiology, biochemistry, microbiology, pathology, pharmacology, surgery, medicine, obstetrics, gynecology, preventive medicine and public health, and psychiatry, this book is a life saver for the busy practitioner faced with necessity of taking a basic science or medical licensure examination. Also an excellent review for comprehensives.

The various subjects are covered by members of staffs of medical schools in different parts of the United States.

The subjects are presented in cleverly condensed paragraphs which make easy reading and in such form as to be easily remembered. Coverage is surprisingly thorough. Questions at the end of each topic represent a condensation of the questions of many state examinations as well as those of the National Boards.

The editor is a former member of the National Board of Medical Examiners and is secretary of the Federation of State Medical Boards of the United States.

WILLIAM J. HULTGEN, M.D.

ESSENTIALS OF DERMATOLOGY. By Norman Tobias, M.D., Associate Clinical Professor of Dermatology, St. Louis University; Fellow, American Academy of Dermatology and Syphililogy; Diplomate, American Board of Dermatology and Syphilology. 4th ed. 596 pages. Illus. Price $6.50. Philadelphia: Lippincott, 1952.

Norman Tobias presents in his fourth edition a clear, concise and well-organized textbook of dermatology. It is intended for the use of general practitioners and medical students who have neither the time nor inclination to refer to larger standard dermatologic references. The different dermatoses are classified and grouped under different chapter headings according to clinical, anatomic, pathologic, and etiologic concepts. Diagnostic criteria are stressed as well as differential diagnosis.

Treatment is discussed for each disease and is brought up to date. Included are the indications for antibiotics, ACTH, and cortisone in certain dermatoses. A unique and very helpful feature of the book are the discussions of the nursing aspects of each group of skin diseases at the end of their respective chapters. No bibliography is available in the book. For its intended purpose as a usable brief and concise reference in the field of dermatology this book fills the bill. One caution: Because of its brevity and necessary limitations one should not expect to practice dermatology in its entirety from such a text.

HAROLD G. RAVITS

Index to Advertisers

Classified Advertising

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *2642 University Avenue, Saint Paul 14, Minn.*

FOR RENT—Attractive doctor's suite in south Minneapolis. Wonderful location for a practice to be built up, or as an outlying office for a downtown doctor. Write Wm. L. Cochrane, 7301 Fremont Avenue South, Minneapolis 19, Minnesota. Telephone RO 9-8758.

WANTED—Midwest Group of twenty physicians have opening for assistant in general surgery including traumatic, industrial and minor injuries; liberal salary depending upon experience or previous training. Address E-330, care MINNESOTA MEDICINE.

WANTED: A general practitioner for Fergus Falls State Hospital. Beginning salary $612 per month. Three bed room house available, partially furnished, subsistence, heated garage, Government working conditions, paid holidays, vacation, sick leave and retirement pension plan. Address inquiries to W. L. Patterson, M.D., Supt., Fergus Falls State Hospital, Fergus Falls, Minnesota.

WANTED—Young general practitioner for new, modern clinic, in rapidly growing Minneapolis suburb. Salary to start, subsequent percentage, possible partnership. Please indicate draft status. Address E-333, care MINNESOTA MEDICINE.

WANTED—Young male pediatrician for expanding group in suburban Minneapolis. State qualifications in first letter. Address E-332, care MINNESOTA MEDICINE.

WANTED—Location for Young General Practitioner. Will buy practice or locate in town needing a doctor. Address E-339, care MINNESOTA MEDICINE.

THORACIC AND GENERAL SURGEON, qualified and certified, age 39, desires location, association or clinic. Straight thoracic surgery preferred. Presently, Chief Surgical Services and Thoracic Surgeon, Veterans Administration Hospital. Write E-335, care MINNESOTA MEDICINE.

EXCELLENT OPPORTUNITY OPENED by death of young doctor; new, well-equipped office building located in shopping center of prosperous farm area in southern Minnesota. A nice place to live! Address E-334, care MINNESOTA MEDICINE.

ATTENTION DOCTORS—Will remodel along modern clinic lines, air-conditioned building with complete facilities for accomodating six physicians. Will give long leases. Excellent Minneapolis location. Address E-336, care MINNESOTA MEDICINE.

WANTED—M.D. for general practice starting January 1, 1953, for two years to replace partner called into service. Small town—small hospital. Address E-337, care MINNESOTA MEDICINE.

WANTED—Young or middle-aged practitioner as associate or locum tenens in large practice near Twin Cities. Eight-room, first-floor clinic. Nurse and office assistant on duty. Good hospital facilities. Large volume with good income. No investment necessary. Excellent opportunity. Address E-338, care MINNESOTA MEDICINE.

WANTED—Young man to assist in general practice near Twin Cities. Hospital facilities available. Well-equipped ground floor office. Permanent association for right man. Address E-340, care MINNESOTA MEDICINE.

PHYSICIAN WANTED as associate in private practice of neurology and psychiatry in Twin Cities. Specialized training not required. Salary open. Address E-341, care MINNESOTA MEDICINE.